(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 02/056948 A1

(51) International Patent Classification[7]: A61M 15/00

(21) International Application Number: PCT/GB02/00198

(22) International Filing Date: 17 January 2002 (17.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0101242.6	17 January 2001 (17.01.2001)	GB
0118789.7	1 August 2001 (01.08.2001)	GB
0129401.6	7 December 2001 (07.12.2001)	GB

(71) Applicant *(for all designated States except US)*: **VECTURA LIMITED** [GB/GB]; University of Bath Campus, Claverton Down, Bath BA2 7AY (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **STANIFORTH, John, Nicholas** [GB/GB]; High Trees, 170 Bloomfield Road, Bath BA2 2ST (GB). **GREEN, Matthew, Michael, James** [GB/GB]; 5 St Lawrence Way, Caterham, Surrey CR3 5FD (GB). **MORTON, David, Alexander, Vodden** [GB/GB]; 2nd Floor Flat, Linsley House, Beechen Cliff Road, Bath BA2 4QR (GB).

(74) Agent: **FRANK B. DEHN & CO.**; 179 Queen Victoria Street, London EC4V 4EL (GB).

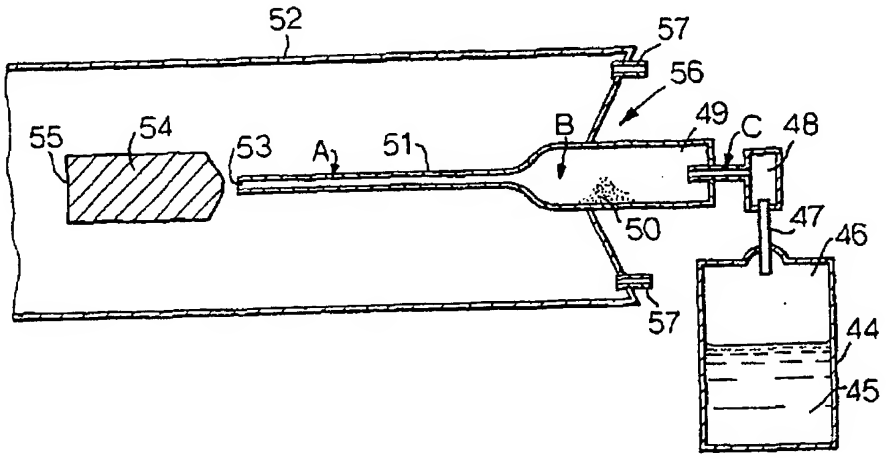
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: AN INHALER DEVICE



(57) Abstract: The invention provides a dry powder inhaler comprising dispensing means for making a dose of a powder available for dispersal, means for generating a jet of gas which, in use, impinges upon or flows across the powder thereby forming a dispersion of the powder in the gas, an impact member located downstream of the means for generating a jet of gas and a mouthpiece located downstream of the impact member.

WO 02/056948 A1

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

An Inhaler Device

This invention relates to inhalers and particularly to powder inhalers.

It has long been recognised that the step of powder entrainment into the air flow through an inhaler can affect the efficiency with which an active substance contained in the powder is delivered to a person's lungs on inhalation. Ideally, upon actuation of the inhaler, all the dose of powder is entrained to form a stable cloud of fine particles which is then inhaled leaving as little as possible of the powder dose remaining in the inhaler. This is especially important where the drug is expensive, for example, a protein drug.

In order that drug particles can be delivered to a person's lungs, and especially to the deep lung, it is important that the size of the particles is small, for example, less than 10μm in diameter. Powders consisting of such small particles tend to be cohesive and to have poor flow properties and therefore tend to be difficult to disperse into an aerosol cloud. In an attempt to improve the situation, some known powders include relatively large particles known as carrier particles which carry fine drug particles upon their surfaces. Other known powders include aggregates of the fine drug particles. For efficient delivery to the lung it is desirable that, during the process of inhalation, aggregates of drug particles are broken up and/or small drug particles are separated from larger carrier particles before they are delivered into the person's respiratory tract.

In an attempt to promote those processes, certain known inhalers include an impact member or impactor against which the flow of the dispersion is directed so that at least some of the powder particles strike the impact member. However, there remains a need for inhaler devices which provide more

efficient deaggregation of the powder.

It has also long been recognised that significant losses of active material can occur through deposition onto, or collision with, the inner surfaces of the mouth or through deposition onto the internal surfaces of the inhaler before the dispersion leaves the device.

The present invention provides a powder inhaler comprising dispensing means for making a dose of a powder available for dispersal, means for generating a jet of gas which, in use, impinges upon or flows across the powder thereby forming a dispersion of the powder in the gas, an impact member located downstream of the means for generating a jet of gas and a mouthpiece located downstream of the impact member.

The mouthpiece preferably communicates with the means for generating a jet of gas so that, when the jet of gas is generated and a dispersion is formed, it can flow through the inhaler to the mouthpiece.

The use of a jet of gas generated by the inhaler makes possible the efficient generation of a powder/gas dispersion traveling at higher velocities than are generally obtainable with conventional inhaler devices which are driven by the users' inhalation. The acceleration of the powder particles to those higher velocities is believed to promote deagglomeration. The combination of the high velocity of the dispersion with an impaction member upon which the dispersion impinges is believed to give particularly effective deagglomeration of agglomerated particles and/or separation of active particles from carrier particles.

The term "dispersal" as used herein refers to the process of suspending at least some of the powder in the jet of gas.

The terms "deagglomeration" and "deaggregation" are used interchangeably herein and refer to the process of separating

agglomerates (aggregates) into individual primary particles. The separation of agglomerates of drug particles into primary particles or the separation of drug particles from carrier particles are both deagglomeration (or "deaggregation") processes as defined herein. Some deagglomeration may occur during dispersal of the powder and in subsequent movement of the dispersion through the inhaler. As mentioned below, the impact member promotes deagglomeration.

The term "dispersal device" as used herein refers to the part of the inhaler which comprises the means for generating a jet of gas and any chambers, passages or other elements which define the zone in which the jet of gas impinges upon or flows across the powder.

The term "inhaler" as used herein should be understood to refer to any device which is suitable for the administration to the lungs of a medicinal formulation in the form of a dry powder.

Preferably, the inhaler will be portable.

The term "jet of gas" as used herein refers to any current of gas having sufficient force to entrain at least some of the powder. Preferably, the jet of gas has a predetermined direction. The term "gas" is to be understood as including propellant vapours, and gases such as dinitrogen monoxide or carbon dioxide, and mixtures of gases such as air. For example, the gas may comprise nitrogen, dinitrogen monoxide, nitrous oxide, carbon monoxide or carbon dioxide. Carbon dioxide is an especially preferred gas. Air is also a preferred gas.

In use of the inhaler, the dispensing means makes a dose of powder available for dispersal, for example, by rupturing a capsule containing a pre-metered dose of powder. The jet of gas then impinges upon the powder (or flows across the top of the powder thereby raising and entraining the powder) thereby

dispersing at least some of, preferably substantially all of, the powder to form a gas stream having entrained within it dispersed particles in varying degrees of agglomeration. That gas stream is referred to herein as a dispersion or a gas/powder dispersion. The dispersion may be formed very quickly if the jet of gas entrains the whole dose at once. Preferably, the arrangement is such that the jet of gas continues and hence the dispersion is formed over a period of time which is advantageously less than the period over which the user inhales and is, for example, from 0.1 seconds to 5 seconds long or, more preferably, from 0.1 seconds to 3 seconds long. Most preferably, the formation of the dispersion commences at least 0.1 seconds after the user has started to inhale through the inhaler and ends not later than 1.5 seconds after the user has started to inhale through the inhaler. Preferably, the dispersion forms a 'bolus' in the inhaled air.

The terms "upstream" and "downstream" as used herein refer to the direction of flow of the dispersion, in use, through the inhaler.

As mentioned above, the use of a jet of gas to disperse the powder makes possible higher gas velocities than can be achieved using only the air flow generated by the user's inhalation, thereby giving more effective dispersal and deagglomeration of the powder particles and making available for inhalation a greater proportion of the dose of the powder. Furthermore, because the jet of gas is generated by a means within the inhaler rather than by the inhalation of the user, the characteristics such as the size and velocity of the jet are independent of the force of the user's inhalation thereby reducing variation between uses of the inhaler in the amount of active substance delivered.

The dispensing means for dispensing a dose of powder may be any means suitable for making available a dose of powder for dispersal. Preferably the means for dispensing a dose of powder is arranged to dispense pre-metered doses of powder, for example, the powder may be contained in blister packs, the blisters being opened either directly in the flow path of the jet of gas or outside the flow path of the jet of gas with the powder dose then being transported into the flow path of the jet of gas. Alternatively, the inhaler may comprise a reservoir for holding the powder and the dispensing means may comprise metering means for metering individual doses of powder from the reservoir.

The jet of gas may be generated by any suitable means. Preferably, the inhaler comprises an orifice, through which, in use, the gas flows under pressure to form the jet (where the inhaler comprises means for generating more than one jet of gas, the inhaler preferably comprises a corresponding number of orifices, through each of which a jet of gas flows). The gas under pressure may be provided by any suitable means, for example, by evaporation of a liquid propellant or from a reservoir of compressed gas such as carbon dioxide, nitrogen or air. Preferably, the gas is under a pressure of at least 0.5 bar over atmospheric pressure.

When the jet of gas is formed by expansion of a compressed gas (as opposed to evaporation of a liquid propellant) the means for generating the jet of gas may comprise a chamber which is supplied with the gas from a reservoir and is kept at constant pressure. The jet of gas is, in that case, formed by allowing gas from the chamber to escape through an orifice. The fact that the chamber is maintained at constant pressure means that the force of the jet of gas will not substantially vary as the amount of gas (and therefore the pressure) in the reservoir decreases due to

repeated use of the inhaler until the pressure in the reservoir drops to a level below that at which the chamber was maintained.

In use of conventional pressurised metered dose inhalers (pMDI's) a suspension of drug particles in a liquid propellant leaves a reservoir via a metering valve and passes into an expansion chamber where it evaporates rapidly to generate an aerosol of the drug particles. In the present invention, liquid propellant (without suspended drug particles) may also be metered into an expansion chamber for evaporation.

Thus, the means for generating a jet of gas may comprise a pressurised reservoir of liquid propellant and an exit valve through which the propellant may leave the reservoir. In use, the propellant evaporates to form the jet of gas. For example, the inhaler may comprise a reservoir of propellant having an exit valve leading to an expansion/evaporation chamber which is provided with an orifice. In use, the valve opens allowing liquid propellant into the evaporation/expansion chamber whereupon the propellant evaporates to form a gas under high pressure for example, a pressure of at least 1.5 bar, preferably 2 bar, more preferably 4 bar. The flow of the gas and any residual evaporating liquid from the orifice generates the jet of gas. Preferably, the expansion/evaporation system provides efficient heat transfer to the propellant thereby ensuring substantially full evaporation of the propellant. The expansion/evaporation system preferably includes metal which allows for efficient heat transfer to the propellant.

Preferably, however, the exit valve communicates with the headspace above the liquid propellant in the reservoir such that, upon actuation of the inhaler, vapour, rather than liquid propellant, passes through the exit valve. That arrangement does not, in principle, require an expansion

chamber having such a high heat transfer capability because the propellant is already in the vapour phase. The arrangement may be such that the gas is not metered by volume, the exit valve being open for a period determined by the inhalation manoeuvre of the user.

Advantageously, the propellant is a propellant known for use with pressurised metered dose inhalers (pMDIs). The propellant may be a single substance or mixture of volatile substances. The propellant preferably does not have significant amounts of non-volatile substances such as excipients and/or active substances dissolved or suspended in it. However, it may in some cases be desirable to include particular excipients, for example signaling agents such as menthol, in the propellant. Preferably, the propellant is selected from the group consisting of chlorofluorocarbons (CFCs), hydrofluorocarbons (HCFs), hydrocarbons (HCs) and hydrofluoroalkanes (HFAs). Advantageously, the propellant is a HFA, for example HFA134a or HFA227. Preferably the propellant comprises one or more substances having a vapour pressure at 20°C of greater than 1.5 bar, more advantageously greater than 2 bar and especially advantageously greater than 4 bar. Preferably the propellant is such that evaporation of the propellant can generate pressures in excess of 2 bar, more preferably in excess of 4 bar.

Additional gases such as carbon-dioxide or dinitrogen oxide (N_2O) may be dissolved in the propellant in order to increase the pressure available to above 4 bar, preferably above 6 bar, more preferably above 10 bar.

Propellants having vapours of relatively high density such as CFC's and HFA's are advantageous because their higher density reduces the rate at which aerosol particles suspended in the vapour will settle out by gravitation, that is, the particles have greater buoyancy in the vapour, than they would

in air. Such vapours of relatively high density (that is, more dense than air) would also be expected to give enhanced turbulence thereby promoting deagglomeration.

It is also thought that the cooling caused by the expansion and/or boiling of the propellant has the beneficial effect of reducing the temperature of the dispersion to a lower temperature than the walls of the inhaler device thereby reducing thermophoretic deposition of the powder particles.

The means for generating a jet of gas may comprise a mechanical pump, for example, a spring loaded piston co-operating with a cylinder. Alternatively, the pump may comprise an impeller driven by an electrical motor.

It has been found that a human inspiration can provide a pressure drop of up to about 10KPa. However, persons having some degree of disease of the lung and the young or old are likely to be able to generate a pressure drop of around only 4 KPa. In contrast, the means for generating a jet of gas will often employ a greater pressure drop, for example, evaporation of a propellant can provide a pressure of over 100 KPa, (for example between 200 and 500 KPa) and so the flow velocities in the inhaler of the invention can be high as compared to flow velocities in conventional dry powder inhalers. At such higher flow velocities, undesirable deposition of the powder in the inhaler is reduced.

It will be appreciated that when a gas flows through an orifice from a region of high pressure to a region of low pressure, the velocity at which the gas flows through the orifice generally increases if the pressure difference between the two regions increased. However, at gas velocities close to the speed of sound the velocity no longer increases with increasing pressure difference and that condition may be referred to as choked flow. Preferably, in use of the inhaler, choked flow conditions occur in the vicinity of, or

downstream of, the zone where the jet of gas impinges on or flows across the powder. The use of choked flow conditions has been found to give more efficient dispersal and deagglomeration of particles.

Advantageously, choked flow conditions occur, in use, in the region of an orifice from which the jet of gas issues. Alternatively, the inhaler comprises, downstream of the zone where the jet of gas impinges on or flows across the powder, a constriction which is so arranged that choked flow conditions occur as, in use, the dispersion of the powder in the gas flows through it. For example, where the zone where the jet of gas impinges on or flows across the powder communicates with the mouthpiece directly via a passage, the passage may have a portion where the walls close together to form a constriction, or the passage may be partially closed by a barrier.

The inhaler may comprise a constriction such as a Venturi throat through which, in use, the dispersion flows or within the vicinity of which the dispersal of the powder in the jet of gas takes place.

Preferably the arrangement is such that the dispersion is generated as inhalation is taking place, that is, the arrangement is preferably such that, in use of the inhaler, the dispersion is formed during the period in which the user of the inhaler inhales from the inhaler. That arrangement allows the total internal volume of the parts of the inhaler through which, in use of the inhaler, the dispersion flows (that is the volume of the passages and chambers between the zone where the jet of gas impinges on or flows across the powder and the mouthpiece) to be small, for example less than $100cm^3$, preferably less than $80cm^3$, advantageously less than $50cm^3$, more preferably less than $25cm^3$ and most preferably less than $15cm^3$. Preferably, the arrangement is such that the

volume of dispersion within the inhaler at one time does not, in use, exceed 80cm^3, preferably less than 50cm^3, more preferably less than 25cm^3 and most preferably less than 15cm^3. Preferably, the inhaler has an internal volume of less than 100cm^3. The zone in which the jet of gas impinges on or flows across the powder may communicate with the mouthpiece by means of a passage. Preferably the internal surface of the passage is smooth and devoid of dead space. The term "dead space" refers to any space or region, for example, regions in the vicinity of angled edges and corners, which is not swept out by gas or air flow when the inhaler is used and in which particles may therefore collect. Advantageously, the inhaler has no "holding volume" in which the dispersion is stationary or almost stationary because under conditions of low flow of the dispersion through the inhaler, particles are liable to be deposited or the internal surfaces of the inhaler. Preferably, in use of the inhaler, less than 10% of the dose of the active agent is deposited inside the inhaler.

The inhaler comprises, downstream of the zone in which the jet of gas impinges on or flows across the powder, an impact member which is situated in the flow path of the dispersion so that the particles are liable to collide with it, thereby promoting deagglomeration. The impact member may also reduce the velocity (that is, the net velocity of the flow as a whole through a plane perpendicular to the overall direction of flow) of the flow of the dispersion. That can be beneficial as, at high flow velocities, impact of the particles with the back of the user's mouth may cause a significant amount of deposition before the particles reach the lung.

The size and location of the impact member is preferably such that, if the impact member were not there, at least 50%, more preferably at least 80% and advantageously essentially

all of the particles would pass through the space to be occupied by the impact member. The presence of the impact member will distort the flow of the dispersion around it. As the gas of the dispersion changes direction in order to flow around the impact member, aerodynamically small particles will be carried with it and so may not collide with the impact member. Larger particles and aggregates of particles having a correspondingly larger momentum will not be as subject to the influences of the gas flow and are therefore more likely to collide with the impact member. In this way, the impact member may act as a size selector for the particles.

Advantageously, the arrangement, (including the size, shape and location of the impact member as well as the velocity and shape of the plume of dispersion) is such that at least 50% of particles having an aerodynamic diameter greater than 10μm collide with the impact member.

Embodiments of the invention having an impact member are particularly suitable for use with formulations comprising carrier particles which are relatively large.

Preferably, the inhaler comprises only one impact member.

The impact member may, together with the internal walls of the inhaler, provide a constriction which promotes turbulent flow of the dispersion. The walls of the passage or chamber in which the impact member is located should, however, be so spaced from the impact member that there is adequate room for the dispersion to flow around the impact member without the flow being restricted to an undesirable degree.

The impact member may present a surface which is substantially perpendicular to the direction of travel of the dispersion immediately upstream of the impact member. The impact member is advantageously substantially rotationally symmetrical about an axis in that direction of flow of the

dispersion. The impact member may consist of or be coated with an anti-adherent material such as Teflon.

The impact member may be held in position by any suitable support members. The support members will advantageously be shaped so as to minimise deposition of powder particles on their surfaces.

Advantageously, downstream of the area in which the jet of gas impinges on or flows across the powder and upstream of the impact member, the device comprises a constriction through which the dispersion flows prior to impinging upon the impact member. The constriction may be the outlet from a cyclonic chamber (see below) and may be arranged in an axial or tangential fashion relative to the cyclonic chamber. The constriction may take the form of a mouth or nozzle shaped so as to direct the flow of the dispersion at the impact member. Advantageously, the constriction takes the form of a tube of reduced internal diameter through which the dispersion flows. The internal diameter of that tube may be in the range of from 0.1mm to 4mm. The tube may be up to 5cm long and is preferably longer than 1mm. The outlet of the tube is arranged directly upstream of the impact member with the impact member being in line with the tube such that, in use, the dispersion exits the tube and impinges upon the impact member. The distance between the outlet of the tube and the impact member is preferably less than 10mm, more preferably less than 5mm and especially preferably less than 2mm. The flow rate of the dispersion within the tube of reduced diameter is relatively fast because of the reduced cross-sectional area of that tube, thereby causing the dispersion to impinge upon the impact member with greater force which promotes the deagglomeration of the powder particles.

The inhaler may comprise means for generating two or more jets of gas for dispersing the powder and where the term "jet of gas" is used herein it should be understood to encompass arrangements wherein there is more than one jet of gas. The use of more than one jet of gas can generate higher levels of turbulence and collisions between particles than are attainable with a single jet and can therefore lead to improved deagglomeration of the particles.

Preferably the inhaler also comprises at least one air inlet which communicates with the zone where the jet of gas impinges upon or flows across the powder and with the mouthpiece, the arrangement being such that, in use, the dispersion of the powder in the gas and air from the atmosphere are combined and are inhaled simultaneously by the user. This arrangement has the advantage that the volume of gas (and therefore the volume of the dispersion produced by the jet of gas) need only be small in relation to the lung capacity of the user, the balance being made up by air sucked though the air inlet which dilutes the gas/powder dispersion, and therefore the size and weight of the inhaler may be reduced compared to the case where the inhaler has no air inlet and the gas produced by the means for generating a jet of gas is the only gas inhaled by the user. Advantageously, the arrangement is such that the volume of the dispersion produced, in use, by the jet of gas is small compared to the volume of air sucked through the air inlet for example, less than 50% and preferably less than 30% of the volume of air sucked through the air inlet. This reduces the chance of the dispersion "blowing back" through the air inlet and being lost to the atmosphere. The dilution of the dispersion with air sucked through the air inlet also reduces the extent of reagglomeration of the particles.

Preferably the arrangement is such that, in use, the air passing through the air inlet or inlets passes along the internal surfaces of the inhaler thereby reducing contact between the dispersed active particles and those internal surfaces. In this way, undesirable deposition of active particles onto the internal surfaces of the inhaler may be minimised.

The zone in which the jet of gas impinges on or flows across the powder and the air inlet or inlets may each communicate with the mouthpiece via separate passages. Preferably, the zone in which the jet of gas impinges on or flows across the powder and the air inlet communicate with the mouthpiece via a common passage, for example, the air inlet may communicate with the mouthpiece via an air flow passage and the zone in which the jet of gas impinges on or flows across the powder may communicate with that air flow passage. In that arrangement, as air is being sucked by the user through the air inlet, the dispersion is being formed by the action of the jet of gas on the powder and mixes with the air in the air flow passage upstream of the mouthpiece. Advantageously, the air flow passage flares outward in the region of mixing of the air with the dispersion, in order to promote mixing of the air and the dispersion.

In a preferred arrangement, the velocity of the dispersion as it impinges upon the impact member is independent of the rate of the user's inhalation. For example, the inhaler may be such that mixing of air drawn in from air inlets (if present) occurs downstream of the impact member and does not influence the flow of dispersion onto the impact member.

The inhaler is preferably one which is designed for use with pre-metered doses of powder, that is, the dispensing means is arranged to dispense pre-metered doses of powder.

The pre-metered doses may, for example, be packaged in a single blister or a plurality of doses may each be packaged in individual blisters on a blister strip or in a series of blister sealed cavities arranged around the circumference of a circular disc. The dispensing means may then comprise mechanical means, for example, a moveable blade or needle, for opening or piercing the blisters and means for advancing the strip or disc between uses of the inhaler.

The pre-metered doses may alternatively be packaged in a plurality of small tubes or wells arranged in a strip or around the circumference of a circular disc. In that case, the dispensing means may comprise mechanical means for opening the tubes at one or both ends. The arrangement of the means for opening the tubes is advantageously such that, in use, release of the powder occurs at a controlled rate over the period of the generation of the jet of gas.

Advantageously, the dispensing means comprises an inlet tube and an outlet tube, the arrangement being such that in use of the inhaler, the jet of gas flows through the inlet tube into a package containing a pre-metered dose of powder and the dispersion flows out of the package through the outlet tube. In a favoured arrangement, the inlet and outlet tubes are arranged to co-operate, in use of the inhaler, with preformed orifices on the package. Accordingly, the invention also provides a package for use with the inhaler which contains a pre-metered dose of powder and has inlet and outlet orifices arranged to co-operate, in use, with one or both of the inlet and outlet tubes of the inhaler. Advantageously, the inlet orifice of the package is less than 2mm, more preferably less than 1mm and especially preferably less than 0.5mm in diameter. The diameter of the outlet orifice may be similar to or less than, but is preferably greater than, the diameter of the inlet orifice. When it is desired to use the inhaler, the

package containing the pre-metered dose of powder is inserted into the inhaler and the inlet and outlet orifices are brought into communication with the inlet and outlet tubes of the dispensing means. The orifices may be covered by removable seals, for example, a foil seal, which are removed by the user prior to the package being fitted to the inhaler. Alternatively, the orifices may be sealed by burstable membranes which are burst by the jet of gas upon actuation of the inhaler.

The inlet and outlet tubes may be movable such that when not in use they are in a storage position and when it is desired to use the inhaler they are moved into engagement with the inlet and outlet orifices of the package.

One, preferably both, of the inlet and outlet tubes may be arranged to be movable so as to penetrate, in use, a penetrable wall of the package, for example, a foil seal. In that arrangement, the package may be kept in a sealed condition until the inhaler is actuated so that the pre-metered dose of powder is protected from the atmosphere for as long as possible. The ends of the inlet and outlet tubes of the dispensing means are preferably sharpened to facilitate the penetration of the penetrable wall of the package. The invention also provides a package for use with the inhaler of the invention which contains a pre-metered dose of powder and has at least one penetrable wall. After use of the inhaler, the spent package is removed from the inhaler and discarded.

The dispensing means may be arranged to feed the whole dose of powder into the zone where the jet of gas impinges on or flows across the powder in a single batch so that the jet of gas impinges on the whole dose at once. However, whilst that arrangement has the advantage of simplicity it is disadvantageous in that the concentration profile of the particles in the gas/powder dispersion produced over the

lifetime of the jet will have a sharp peak and will then die away quickly. Such a "pulse" of highly concentrated powder may be unpleasant for the user and, furthermore, the likelihood of particle reagglomeration within that "pulse" is increased because the particles are closer together than they would be if the powder dose was fed into the jet of gas gradually over a period of time, and therefore there exists an increased probability of the particles colliding with each other.

Preferably, the dispensing means comprises a feed device for incremental feeding of the powder, in use, into the jet of gas. The term "incremental" as used herein includes the gradual dispensing of the dose in a number of small portions as well as the continuous dispensing of the dose over a period of time. Such incremental feeding may be, for example, by controlled release of powder from a tube, preferably a narrow tube. A similar result may be obtained by the use of a 'fluidised bed' as described below.

In use, actuation of the inhaler triggers generation of the jet of gas. The jet of gas will last for a period of time which is generally not longer than the period of time over which the user can comfortably inhale, for example, the jet of gas may last for between 0.1 and 5 seconds, preferably from 0.5 to 3 seconds and most preferably between 1 and 2.5 seconds. The feed device may feed powder into the jet of gas continually during the time the jet of gas is being generated.

Preferably, the powder feed may end before the generation of the jet of gas ends by, for example 0.1 or 0.5 seconds, so that towards the end of the period of generation of the jet of gas, no new powder is introduced and the jet can sweep the internal surfaces of the inhaler clean of powder.

The feed means may comprise a plunger which, in use, pushes the powder from a holder. The holder will have an

internal cavity for the powder with a cross section which corresponds to the shape of the plunger in a plane perpendicular to the direction of travel, for example, the holder may be annular and the plunger circular. The dispensing means may, where the powder dose is pre-metered and packaged in a tube, comprise means for opening at least one end of the tube, means for positioning the tube in the region of the jet of gas and means for incrementally pushing the powder dose from the tube. Alternatively, the tube may form part of a metering arrangement for metering powder from a reservoir. The dispensing device may comprise a linear or circular strip, which holds the powder evenly spread and which is arranged to move incrementally through the jet of gas. The strip may be textured to hold powder, for example, the strip may be grooved.

Preferably the inhaler comprises means for imparting a helical form to the flow of the dispersion. For example, the inhaler may comprise a chamber of circular cross section having a tangentially arranged inlet or having angled blades to direct the flow in a helical manner. The dispersion may be generated in the chamber, in which case the tangential inlet will be an inlet for the jet of gas and powder will either be present in the chamber before the jet of gas begins to flow, or will be fed into the chamber during the period in which the jet of gas flows. Alternatively, the dispersion may be generated upstream of the chamber, in which case the dispersion will, in use, flow into the chamber through the inlet. In a preferred embodiment, the chamber is formed in a replaceable dose package so that, after use, the package and the chamber may be discarded thereby avoiding any need to clean the chamber. The chamber is preferably cylindrical. The chamber preferably has a diameter in the range of 4mm to 30mm. The inlet into the chamber may be less than 2mm, preferably

less than 1mm and more preferably less than 0.5mm in diameter, The outlet is preferably axially arranged relative to the chamber. The diameter of the outlet may be similar to or less than, but is preferably greater than, the diameter of the inlet.

The means for imparting helical flow may be a spiral tube through which the dispersion flows. The means for imparting helical flow may be of, or be coated with, an anti-adherent material such as Teflon.

The means for imparting a helical flow to the dispersion may be arranged downstream of the zone where the jet of gas impinges on or flows across the powder and upstream of the mouthpiece.

The means for imparting helical flow is advantageously upstream of the impact member such that the flow of the dispersion as it impinges upon impact member is at least partially helical. The means for imparting helical flow may be downstream of the impact member. The means for imparting a helical flow to the gas may also be arranged upstream of the region where the gas impinges upon the powder (it has been found that the helical flow may in some cases continue downstream of that region). The means for imparting helical flow to the gas may also be arranged downstream of the region where the gas impinges on the powder and, in some cases, that arrangement has surprisingly been found to produce helical flow in that region.

Where the inhaler is an inhaler arranged to use a package comprising a pre-metered dose of powder, as described above, the package may comprise means for imparting a helical flow to the dispersion. For example, the package may comprise a chamber of circular cross-section having a tangentially arranged inlet or having angled blades to direct the flow in a helical manner as described above. Such packages are another

aspect of the invention. Preferably, the package is of an anti-adherent material such as Teflon. Alternatively, the internal walls of the package may be coated with an anti-adherent material.

Helical flow of the dispersion is thought to promote the dispersal and deagglomeration of the active particles. Where helical flow of the dispersion occurs in a chamber as described above, larger particles, for example, carrier particles or agglomerates will tend to be thrown toward the outside of the vortex whereas fine particles, for example, active particles will tend to move toward the centre of the vortex, that is, toward the axis of rotation. Collisions with the chamber walls or with other particles may cause the large particles to break up or deagglomerate into fine particles which will then move toward the centre of the vortex. Where the exit from the chamber is aligned with the centre of the vortex, the fine particles will be more likely to be carried through that exit than the large particles rather in the manner of a cyclone separation unit. In that way the large particles may be retained within the chamber whilst the active particles leave the chamber. Where the chamber is part of a replaceable package, the retained large particles will be discarded along with the spent package. The retention of the large particles will be more efficient as the size of those particles is increased and is likely to be especially advantageous where the particles are larger than conventional carrier particles, for example, when the carrier particles are fissured carrier particles. Whilst devices to promote helical flow are known for use with conventional dry powder inhalers, they suffer from the problem of powder deposition within the device. In the inhaler of the present invention, the flow rates are in general higher than that which can be obtained in

a conventional DPI by the user's inhalation and therefore undesirable deposition in the inhaler is reduced.

Preferably, the inhaler comprises a chamber containing a plurality of relatively large particles, the chamber having an inlet for the jet of gas, an inlet for the powder and an outlet for the dispersion which communicates with the mouthpiece, the inlets and the outlet having mesh means to retain the relatively large particles within the chamber and the arrangement being such that, in use, the gas agitates the relatively large particles. In this way, in use of the inhaler, the relatively large particles form a fluidised bed. The gas flow through the bed creates shear on the particles thereby aiding dispersal and deagglomeration. Furthermore, the powder will be released from the fluidised bed over a period of time, for example, over a period of from 0.5 to 1.5 seconds in duration, rather than in a single batch or "pulse" and will therefore provide, at least in part, the benefits associated with incremental feeding of the powder as discussed above.

The term "relatively large particles" refers to particles significantly larger than the powder particles, for example, of diameter greater than 0.2 mm, preferably greater than 0.5 mm. The relatively large particles may be beads having smooth surfaces. The relatively large particles may be of ceramic, for example zirconia or alumina or of glass or metal. Alternatively, the relatively large particles may be of a pharmaceutically inert excipient material, for example, a crystalline sugar such as lactose or a polymeric material. Preferably, all inlets and outlets to and from the chamber are covered with filtering means, for example, mesh, to retain the relatively large particles in the chamber.

Preferably the powder is dispensed before generation of the jet of gas is commenced. The jet of gas flows through the

inlet for the gas and impinges onto the powder and the relatively large particles, thereby producing a fluidised bed. Optionally, the chamber may comprise a vibrating member which enhances the motion of the relatively large particles.

The inhaler may comprise a chamber located downstream of the zone in which the jet of gas impinges upon or flows across the powder, the chamber containing a plurality of relatively large particles and having an inlet through which, in use, the dispersion enters the chamber and an outlet through which, in use, the dispersion leaves the chamber, the inlet and outlet having mesh means to retain the relatively large particles within the chamber and the arrangement being such that, in use, the gas agitates the relatively large particles. The passage of the dispersion through the chamber agitates the beads, the motion of which promotes the deaggregation of the powder particles. The chamber may be upstream or downstream of the impact member.

Preferably the inhaler comprises, downstream of the zone in which the jet of gas impinges on or flows across the powder, means for subjecting the dispersion, in use, to converging currents of gas. Preferably, the currents of gas flow in opposing directions. In this way, turbulence is generated in the dispersion which improves the dispersal and deaggregation of the particles. Preferably, the opposing currents are currents of gas/powder dispersion. Impacts between the particles will increase deagglomeration of the particles. Preferably, the arrangement is such that fine particles are separated in a centrifugal flow area and carried downstream to the mouthpiece whilst larger particles or agglomerates are recycled back to the impaction zone. Such arrangements are known for use in jet mills. This arrangement is particularly suitable for use in an inhaler comprising

means for generating a jet of gas because of the high flow rates which may be produced by the jet.

It is known that the proportion of an inhaled dose of powder which reaches the lower lung varies with the rate of inhalation. At high flow rates, the particles are more likely to have a high momentum which causes them to impact with the walls of the respiratory tract prior to entry to the lower lung. Advantageously, the inhaler includes means for restricting the flow rate through the mouthpiece to not more than 80 litres/minute, preferably not more than 60 litres/minute and more preferably to not more than 40 litres/minute. Such a restricted flow rate helps to ensure that the user takes a relatively long, slow inspiration which is believed to be beneficial. Where the inhaler has an air inlet and the arrangement is such that air drawn through that inlet makes up the major proportion of the inhaled breath, the restriction means may take the form of a constriction in the vicinity of or downstream of the air inlet. Where the inhaled gas comprises a major proportion of the gas making up the jet of gas the restriction means may take the form of a means for limiting the rate of production of gas, for example, where the gas is produced by evaporation of a liquid propellant contained in a reservoir having an exit valve, the exit valve may be sized so as to maintain the gas flow rate below the desired maximum.

The inhaler may be actuated by the user. For example, the user may place the mouthpiece in his or her mouth and press a button to actuate the dispensing means and the generation of the jet of gas. However, in that arrangement, it is necessary for the user to co-ordinate inhalation with the pressing of a button, especially in the case where the inhaler has an air inlet for inhaled air, and some types of users, particularly the young, find that coordination

difficult to achieve. Preferably, the inhaler is actuated upon inhalation through the mouthpiece, that is, the jet of gas is actuated by the inhalation. For example, where the inhaler has an air inlet, it may comprise a biassed hinged gate in the region of or downstream of the air inlet which is connected to the means for generating the jet of gas and is arranged to be moved by air sucked in through the inlet, thereby triggering generation of the jet of gas. Where the inhaler does not have an air inlet, generation of the jet of gas may be triggered by a pressure sensor which responds to the drop in pressure caused by inhalation of the user through the mouthpiece. The arrangement may be such that generation of the jet of gas may continue for as long as the user inhales or it may be such that generation of the jet of gas continues for a fixed period. Where the inhaler has an air inlet, the arrangement may be such that the generation of the jet of gas and consequent dispersal of the powder in the dispersing means has a fixed duration which is shorter than the expected duration of the user's inhalation thereby providing for a bolus cloud comprising the dispersed particles to be generated, delivered and followed by clean air before inhalation ceases. For example, the arrangement may be such that upon inhalation through the mouthpiece the jet of gas is generated and continues to be generated for between 0.1 and 5 seconds, preferably between 0.5 and 3 seconds and more preferably between 1 and 2 seconds.

Such automatic actuation on inhalation means that the dispersion is generated on demand, travelling very quickly into the user's airways with minimum exposure to the device's internal walls. As the dispersion continues to be generated while the user is inhaling, the total volume of dispersion generated can be quite large (but not exceeding the user's inhalation volume) while avoiding the need for a

correspondingly large chamber within the inhaler. The generation of a large, dilute dispersion is also advantageous compared to a smaller, more concentrated dispersion because the likelihood of particle reagglomaration is reduced.

The mouthpiece may be of any suitable form. It is known that upon inhalation of a dispersion of particles, a proportion of the particles is deposited on the inside of the mouth, for example, on the tongue. Preferably, the mouthpiece is adapted to extend, in use, past the teeth of the user and over at least a portion of the user's tongue, for example, over a quarter or more preferably over half the length of the tongue. Especially, advantageously, the mouthpiece comprises external stop members which, in use, abut the lips or the teeth of the user. Such stop members allow the user to correctly and reproducibly position the mouthpiece in his or her mouth.

In a preferred embodiment, the invention provides a dry powder inhaler comprising dispensing means for dispensing a dose of a powder, means for generating a jet of gas which, in use, impinges upon or flows across the powder thereby forming a dispersion of the powder in the gas, a mouthpiece located downstream of and communicating with the means for generating a jet of gas and, downstream of the means for generating a jet of gas and upstream of the mouthpiece, an impact member and means for imparting helical flow of the dispersion, the arrangement being such that, in use of the inhaler, the dispersion is formed during the period over which the user of the inhaler inhales from the inhaler. Advantageously, the helical flow takes place in a chamber having a circular or oval cross-section, for example, a cylindrical chamber or tube, which may have a conical section at one end.

The invention provides an inhaler comprising dispensing means for making a dose of a powder available for dispersal, a

dispersal device comprising means for generating a jet of gas which, in use, impinges upon or flows across the powder thereby forming a dispersion of the powder in the gas, the inhaler further comprising an impact member located downstream of the dispersal device and a mouthpiece located downstream of the impact member and communicating with the dispersal device.

The invention also provides an inhaler comprising dispensing means for dispensing a dose of a powder, a dispersal device comprising means for generating a jet of gas which, in use, impinges upon or flows across the powder thereby forming a dispersion of the powder in the gas and a mouthpiece located downstream of and communicating with the dispersal device, the arrangement being such that in use of the inhaler the dispersion is formed during the period over which the user of the inhaler inhales from the inhaler. In this aspect, the inhaler does not comprise an impact member but may comprise one or more of the other features mentioned herein.

The invention also provides an inhaler including a replaceable package comprising a pre-metered dose of powder as described above.

Powders suitable for use with an inhaler according to the invention preferably comprise one or more pharmacologically active agents. Suitable pharmacologically active agents may be substances for therapeutic and/or prophylactic use. Active agents which may be included in the formulation include those products which are usually administered orally by inhalation for the treatment of disease such as respiratory disease, for example, ß-agonists.

The active agent may comprise at least one $ß_2$-agonist, for example one or more compounds selected from terbutaline, salbutamol, salmeterol and formeterol. If desired, the powder may comprise more than one of those active agents, provided

that they are compatible with one another under conditions of storage and use. Preferably, the active agent is salbutamol sulphate. References herein to any active agent is to be understood to include any physiologically acceptable derivative. In the case of the B_2-agonists mentioned above, physiologically acceptable derivatives include especially salts, including sulphates.

The active agent may be ipratropium bromide.

The powder may include a steroid, which may be beclomethasone dipropionate or may be Fluticasone. The active principle may include a cromone which may be sodium cromoglycate or nedocromil. The active principle may include a leukotriene receptor antagonist.

The powder may include a carbohydrate, for example heparin.

The powder may advantageously comprise a pharmacologically active agent for systemic use provided that it is capable of being absorbed into the circulatory system via the lungs. For example, the powder may comprise proteins, peptides or polypeptides such as DNase, leukotrienes or insulin, leuprolide, growth hormone, parathyroid hormone or an interferon. The formulation of the invention may in particular have application in the administration of insulin to diabetic patients, thus avoiding the normally invasive administration techniques used for that agent. The technique could also be used for the local administration of other agents for example for pain relief (e.g. analgesics), anti cancer activity, anti-virals, antibiotics or the local delivery of vaccines to the respiratory tract.

The active agent may be in the form of primary (that is, undivided) particles which advantageously have a mass median aerodynamic diameter in the range of from 0.1 to 15μm, preferably from 0.1 to 10μm, more preferably from 1 to 8μm and

most preferably from 0.5 to 2μm. The active particles are present in an effective amount, for example, at least 0.01% by weight, and may be present in an amount of up to 100% by weight based on the total weight of the powder. Preferably, the active agent is in the form of particles having a geometric standard deviation of aerodynamic diameter of less than 1.8, more preferably less than 1.6 and especially advantageously less than 1.4.

The powder may comprise carrier particles. The carrier particles may be conventional carrier particles having a mass median diameter (MMD) of around 90μm. Preferably, however, the carrier particles have an MMD of at least 175μm, more preferably at least 200μm and especially preferably at least 250μm. The carrier particles may have a diameter of at least 50μm. Although as described below the formulation may include particles of diameter less than 50μm of the same material as the carrier particles, those smaller particles are not included within the term "carrier particles" as used herein. Advantageously, not more than 10% by weight, and preferably not more than 5% by weight, of the carrier particles have a diameter of 150μm or less. Advantageously at least 90% by weight of the carrier particles have a diameter of 175μm or more, and preferably 200μm or more. Advantageously, at least 90% by weight, and preferably at least 95% by weight, of the carrier particles have a diameter of not more than 1mm. Preferably at least 90% by weight of the carrier particles have a diameter of not more than 600μm. Advantageously, at least 50% by weight, and preferably at least 60% by weight, of the carrier particles have a diameter of 200μm or more. Preferably, at least 90% by weight of the carrier particles have a diameter between 150μm and 750μm, more preferably between 150μm and 650μm. Particular advantages are offered by

formulations in which substantially all of the carrier particles have a diameter in the range of about 210 to about 360μm or from about 350 to about 600μm.

The carrier particles may be of any acceptable pharmacologically inert material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols; polyols, for example sorbitol, mannitol and xylitol, and crystalline sugars, including monosaccharides and disaccharides; inorganic salts such as sodium chloride and calcium carbonate; organic salts such as sodium lactate; and other organic compounds such as urea, polysaccharides, for example starch and its derivatives; oligosaccharides, for example cyclodextrins and dextrins. Advantageously the carrier particles are of a crystalline sugar, for example, a monosaccharide such as glucose or arabinose, or a disaccharide such as maltose, saccharose, dextrose or lactose. Preferably, the carrier particles are of lactose.

The carrier particles are preferably of a material having a fissured surface, that is, on which there are clefts and valleys and other recessed regions, referred to herein collectively as fissures. Such carrier particles are described in PCT/GB01/01732 published as WO 01/78694. The fissures should preferably be a least 5μm wide extending to at least 5μm deep, preferably at least 10μm wide and 10μm deep and most preferably at least 20μm wide and 20μm deep. The fissured carrier particles offer particular advantages in that they are capable of retaining relatively large amounts of fine material in the fissures without or with only little segregation. Those fissured carrier particles may have been produced by wet agglomeration of smaller carrier particles and may, at least to some degree, also be broken up in the inhaler by turbulent flow and impacts into smaller particles.

It is believed that including carrier particles in a powder for inhalation may provide the following benefits:

1) The process of suspending and aerosolising the powder is enhanced, thereby helping to empty the inhaler device;

2) The greater momentum and kinetic energy of carrier particles (as compared to fine active particles) in motion enhances deaggregation of the particles in the powder, particularly deaggregation arising through impact of the particles with the inhaler surfaces or with other particles;

3) The carrier particles improve the flow properties of the powder; and

4) The carrier powders help to scour powder deposits from the internal surfaces of the inhaler.

It will be appreciated that those benefits will be more evident for larger carrier particles than for relatively small carrier particles.

The powder may comprise an additive material which promotes the dispersal of the particles of active agent. Such additive materials are described in WO 96/23485 and WO 97/03649. The powder may further comprise fine particles of an excipient material, that is, fine particles of a solid, pharmaceutically inert substance.

In addition to any carrier particles, active agent, additive material and fine excipient particles, powders suitable for use in an inhaler according to the invention may comprise one or more further additives suitable for use in inhaler formulations, for example, flavourings, lubricants, and flow improvers. Where such further additives are present, they will generally not exceed 10% by weight of the total weight of the formulation.

The small size of the active particles is associated with a tendency to form agglomerates or to adhere to the surfaces of larger particles if present, for example carrier particles.

As noted above, the deagglomeration of the active particles is considered to be an important step in the delivery of the active particles to the lung. The action of the jet of gas upon the powder, as well as causing effective resuspension and dispersal of some or all of the powder, also has the desirable effect of causing, to a greater or lesser extent, deagglomeration of the active particles. The inhaler may contain one or more doses of a formulation having one or more of the features described above. The inhaler advantageously comprises one or more doses of a formulation comprising carrier particles, especially fissured carrier particles.

The invention also provides a method of generating a dispersion in a powder inhaler comprising the steps of

1) making a dose of powder available for dispersal;

2) generating a jet of gas under positive pressure which impinges upon or flows across a powder thereby forming a dispersion of the powder in the gas; and

3) directing the flow of the dispersion onto an impact member.

The term "positive pressure" refers to a pressure above atmospheric pressure (>1bar), for example, greater than 1.5 bar.

The jet of gas is preferably generated while inhalation is taking place. Preferably, the jet of gas is generated by allowing gas under a pressure above atmospheric to flow through an orifice to a region of atmospheric pressure.

Several embodiments of the invention will now be described for the purpose of illustration only with reference to the Figures in which:

Figure 1 shows vertical sectional view of an inhaler according to the invention;

Figure 2 shows a plan view of a wheel of dosing wells for use in the dispersal mechanism of Figure 3,

Figures 3 to 6c show various forms of dispersal device for use with inhalers according to the invention, and

Figures 7 and 8 show two forms of chamber comprising relatively large particles for use with inhalers according to the invention.

Figure 9 shows a dispersal device with an expansion chamber,

Figures 10a and 10b show two dispersal devices each arranged to generate a jet of gas from vapour released from the headspace in a reservoir,

Figures 11a to 11d show various forms of impact member,

Figures 12a and 12b are, respectively, a front view and side view in section of a chamber having a tangential inlet,

Figures 13a and 13b are, respectively, front and side views in section of another chamber having a tangential inlet,

Figures 14a and 14b are, respectively, a side view and a front view in section of a separation device in an inhaler,

Figures 15a and 15b are a front and side view in section, respectively, of a chamber having blades for imparting a helical flow,

Figure 16 shows in section a part of an inhaler having angled air inlets to promote helical flow,

Figure 17 is an end view of the air inlets of figure 16,

Figure 18 shows a tube, part of which has a spiral form,

Figure 19 shows a part of an inhaler having an expanded region around an impact member,

Figure 20 shows a disposable package containing a pre-metered dose of powder,

Figure 21a shows a view of another disposable package containing a pre-metered dose of powder,

Figure 21b shows an end view of the package shown in Figure 21a,

Figure 22a shows in perspective view a further disposable package containing a pre-metered dose of powder, and

Figure 22b shows a view from the top of the package shown in Figure 22a.

Figure 1 shows a dry powder inhaler comprising a casing 1, which surrounds a reservoir bottle 2 for liquid propellant or compressed gas having an exit valve 3 which leads via a tube 4 into evaporation chamber and a heat exchange unit 5. The evaporation chamber has an exit orifice 6 which leads directly to a tube 7. The tube 7 has two parts 7a and 7b, arranged along a common axis. A gap between those two parts 7a and 7b accommodates a dose wheel 8 (see Figure 2) which turns about a spindle 9. The tube 7b joins on to an air flow passage 10 which extends between an air inlet 11 and a mouthpiece 12. At the exit of tube 7b into air flow passage 10 is an impact member (not shown in Figure 1) fixed in a position such that the plume of dispersion leaving the tube 7b impinges upon it. Collisions between the powder particles and the impact member promote deagglomeration of aggregates in the powder and, where the powder comprises carrier particles, separation of the active particles from the carrier particles.

The air flow passage 10 has a region of increased diameter in the vicinity of the union with the tube 7b to reduce contact between the particles and the walls of the air flow passage 12, thereby discouraging powder deposition on those walls.

Air inlet 11 may be provided with a gate arranged to move in response to air being sucked in through the air inlet 11, and a control mechanism arranged to trigger the opening of the valve 3 in response to that movement of the gate. Alternatively, an actuation button for the opening of the valve 3 may be provided on the casing 1.

In use, the user inhales through the mouthpiece 12 which, if the air inlet 11 is provided with a trigger gate, automatically causes the valve 3 to open. Otherwise the user presses an actuation button on the casing while inhaling which causes the valve 3 to open. The opening of the valve 3 allows liquid propellant to flow out of the reservoir 2 under pressure and into the chamber 5 whereupon it evaporates to generate gas under high pressure. That gas flows through the orifice 6 to form a jet of gas in the tube 7a which impinges on powder held in a holder 8a of the dose wheel 8, dispersing the powder and sweeping it into the tube 7b. As the dispersion leaves tube 7b it impinges on the impact member (not shown) and then flows into the air flow passage 10. The gas/powder dispersion exiting the tube 7b is entrained in the larger volume of air being sucked through the air inlet 11 along the flow passage 10 and out of the mouthpiece 12. The mouthpiece 12 comprises stop members 12a which rest against the front of the user's teeth during inhalation, an extended portion 12b, which extends past a significant portion of the user's tongue, and outlet 12c.

The high pressure of the gas in the chamber 5 ensures that the jet of gas in the tube 7a travels at a high velocity thereby giving excellent dispersal of the powder in the holder 8a. That dispersal and deagglomeration is particularly efficient where the pressure of the gas in the chamber 5 and the diameter of the orifice 6 are such that choked flow conditions occur in the tube 7. The velocity of the dispersion in tube 7b is also high and therefore agglomerates or large carrier particles present in the dispersion strike the impact member with a high degree of force.

The dose wheel 8 is shown in plan view in Figure 2 and comprises about its circumference a plurality of dose holders 8a each holding a pre-metered dose of powder. Upon each

actuation of the inhaler, the dosing wheel 8 rotates to bring a new holder 8 into alignment with the tubes 7a and 7b.

Figure 3 shows a portion of an inhaler wherein the dosing wheel 8 comprises a plurality of tubular holders 13 open at each end. The dosing wheel rotates between a powder reservoir (not shown) where the holders 13 are filled with powder and chamber 14 thereby transporting doses of powder from the reservoir to the chamber 14. Chamber 14 is of generally conical form and has an inlet 15 arranged at the wide end of the cone through which the jet of gas enters and an axial outlet 16 at the narrow end of the cone through which the gas/powder dispersion exits. The dosing wheel 8 extends into the chamber 14 such that the holder 13 is located along the axis of the cone between the inlet 15 and the outlet 16. In use, the jet of gas flows over the top of the holder 13 and the powder is pushed incrementally from the holder 13 into the path of the jet of gas by a plunger 17 which extends through one wall of the chamber 1.

The inlet 15 may be radially arranged so that the jet of gas flows directly toward the holder 13. Preferably, however, the inlet 15 is tangential to the chamber 14 so that the jet of gas flows about the chamber 14 in a helical fashion.

The outlet 16 has constriction 18 in which choked flow conditions occur as the gas/powder dispersion flows through it. Downstream of the constriction 18 is an impactor plate 18a with which particles collide, thereby promoting deagglomeration. The impactor plate 18a is located directly in the flow path of the plume of dispersion which exits the constriction 18.

Figures 4 and 5 show details of two further arrangements for incremental feeling of the powder into a jet of gas.

Figure 4 shows a turntable 19 upon which powder is evenly spread. In use, a jet of gas issues from a tube 20 which is

directed toward the circumference of the turntable 19, sweeping the powder from a portion of the turntable 19 as a dispersion in the direction of the arrows A. The turntable 19 rotates about a spindle 21 bringing more powder into contact with the jet of gas. The turntable 19 completes one rotation in two seconds.

Figure 5 shows another turntable arrangement wherein the powder is contained in holders (not shown) arranged in the body of wheel B and open at the circumference of wheel B. In use, gas flows along tube 20 and issues as a jet from orifice 22, sweeping powder from the tubular holders as the wheel 8 rotates.

Figure 6a shows a form of constriction comprising conical impact member 23 arranged coaxially with conically tapered tube 24 to provide a conical annular flow path downstream of powder dispenser 25. In use, a jet of gas is formed through tube 24, dispersing and entraining powder from dispenser 25 to form a gas/powder dispersion. Lateral velocity gradients in the flow path produce shear which promotes dispersal and deagglomeration of the particles.

Figure 6b shows a modification of the apparatus of Figure 6a in which the conical impact member 23 is located immediately downstream of an outlet 24a from a generally cylindrical chamber 24b. The outlet 24a is axially arranged in one end of the chamber 24b. At the other end of the chamber 24b is inlet 24c which is tangentially arranged with respect to the chamber 24b. In use, the jet of gas enters the chamber 24b through inlet 24c and swirls in a helical fashion down the chamber as shown in Figure 6b. Upon leaving the chamber 24b via axial exit 24a, the dispersion impinges upon conical impact member 23.

The powder may be introduced through a powder inlet tube at the position marked by arrow A into inlet tube 24a or it

may be introduced through a powder inlet tube directly into chamber 24b at the position marked by arrow B. Alternatively, the chamber 24b may be formed as part of a replaceable package containing a pre-metered dose of the powder. In that embodiment, the package is fitted to the inhaler so that the inlet 24c connects to the gas supply device and the exit 24a is correctly positioned relative to the impact member 23. The inhaler is then ready for actuation. The package is discarded after use.

Figure 6c shows an arrangement which is similar to that shown in Figure 6b but wherein the exit 24a is tangential to the chamber 24b.

Figure 7 shows a fluidisation chamber 33 having a powder inlet tube 34, a porous floor 35 through which a jet of gas may flow and an outlet 36 which is covered by a mesh 37. The chamber contains zirconina beads 38. Prior to actuation of the inhaler, the beads 38 rest on the porous floor 35. Upon actuation of the inhaler, a dose of powder is dropped through the inlet 34 onto the beads 38 and a gas jet is caused to flow through the porous floor 35 agitating the beads 38 in the manner of a fluidised bed. The powder (not shown) is dispersed by the combined action of the gas jet and motion of the beads 38 and exits the chamber as a gas/powder dispersion through outlet 36.

Figure 8 shows an embodiment wherein a gas/powder dispersion is formed outside of chamber 33 by gas jet in tube 34 impinging on powder being dispensed from tube 35. The gas/powder dispersion enters chamber 33 through a tube having an open end close to the floor of chamber 33. As the dispersion is forced into chamber 33 it agitates the beads 38 thereby improving the dispersal and deagglomeration of the particles.

Figure 9 shows a partial side view of a section through a dispersal device in an inhaler according to the invention. The dispersal device comprises expansion chamber 39 having at one end an inlet 40 leading to a valve and reservoir (not shown) of liquid propellant. At the other end of chamber 39 is a tapered section 41 which leads to venturi 42 having powder inlet 43. Immediately beyond the venturi 42 is impact member 42a. In use, upon actuation of the inhaler, a predetermined volume of liquid propellant is metered from the reservoir (not shown) via the metering valve (not shown) into the chamber 39 via inlet 40. The propellant then evaporates rapidly producing a jet of gas through venturi 42 which entrains powder from the powder inlet 43 to form a dispersion. The dispersion strikes imact member 42a upon leaving venturi 42, thereby promoting deagglomeration of the powder. The dispersion then flows toward the mouthpiece (not shown).

Figure 10a shows a dispersal device comprising a reservoir 44 containing liquid propellant 45, for example a hydrofluoroalkane propellant, and having headspace 46 above the propellant. A tube 47 leads from the headspace 46 to a valve 48 which communicates with a chamber 49. Powder 50, which may be a pre-metered dose of powder, is present in chamber 49. (Powder may also be introduced via a powder dosing wheel as shown in Figure 2. The powder dosing wheel would be arranged to rotate about an axis parallel to the axis of the tube 51 and could be arranged to introduce powder at locations A, B or C as shown). Chamber 49 leads into an extended narrow tube 51 which itself extends along the axis of a cylindrical outer tube 52. Downstream of the open end 53 of the tube 51 is an impact member 54 of generally cylindrical shape which is fixed to the walls of outer tube 52 by support struts (not shown). The leading surface of impact member 54

has a central, flat portion (which directly opposes the open end 53 of tube 54) and angled shoulders.

Upon actuation of the inhaler, the valve 48 is opened for a predetermined period of time allowing propellant vapour to escape into the chamber 49 forming a jet which flows over the powder 50 generating a powder dispersion which flows under pressure along the tube 50. Upon leaving the open end 53 of the tube 50 the dispersion impinges upon the leading surface of the impact member 54 and larger particles and aggregates with sufficient momentum will strike that surface. Separation of the active particles from carrier particles and the breaking up of aggregates is promoted both by those collisions with the impact member and by the turbulence around the impact member.

The trailing (i.e. downstream) surface 55 of the impact member 54 is flat and is perpendicular to the direction of flow of the dispersion. Further turbulence is generated as eddies form in the region of the downstream end of the impact member 54, thereby serving to further disperse the active particles.

In one favoured embodiment, the upstream end 56 of the outer tube 52 includes a pressure sensor for sensing a pressure drop caused by the user inhaling through the mouthpiece (not shown). The signals from that sensor can be used to initiate opening of the valve 48 such that the generation of the dispersion is actuated by the user's inhalation.

In a further favoured embodiment, the upstream end region 56 of outer tube 52 comprises air inlets 57. Those air inlets may be arranged around the outer wall of outer tube 52 so that air drawn in by the user's inhalation flows down the outer tube 52 along the inside wall of that tube thereby reducing contact between the dispersed powder and the walls of the

outer tube 52 with a consequent reduction in deposition of the particles on those walls.

Figure 10b shows an arrangement generally similar to that shown in Figure 10a with two modifications. Firstly, the tube 48a which connects valve 48 with chamber 49 is arranged in an tangential direction to the chamber in the manner shown in Figures 12 a) and b) such that the propellant vapour flows, in chamber 49, in a swirling helical fashion. Secondly, air inlets 57a, are arranged in the wall of tube 52, rather than at the upstream end of that tube, and are arranged to direct the flow of air toward the expanding powder bolus exiting from tube 53.

Figures 11a to 11d show side views of four impact members of differing shapes for use in the device of figure 10. The impact member shown in figure 11a has a leading (upstream) surface having a central flat portion and angled shoulders similar to the impact member 54 shown in figure 10. However, the impact member of figure 11a is not cylindrical but is generally conical so that it tapers away in the downstream direction to a point. That tapering is believed to minimise powder deposition on the downstream portion of the impact member. The impact member of figure 11b has the form of a truncated cone with the narrow end pointing upstream so that the dispersion impinges upon the small flat portion and then flows along the outwardly tapering body of the impact member. The tapered nature of that impact member in the upstream region where the dispersion first impinges upon it reduces the likelihood of particles being thrown against the inner walls of outer tube 52.

Figure 11c shows an impact member of generally cylindrical form but having a rounded leading surface. The rounded end may be embossed with a spiral pattern, for

example, it may have spiral grooves, in order to impart a helical flow to the dispersion.

Figure 11d shows a small, cylindrical impact member having a cross-section corresponding to that of the elongated tube 50. The small size of the cross section is again thought to reduce the likelihood of particles contacing the walls of the outer tube 52. The gap between the open end 53 of the tube 50 and the upstream surface of the impact member shown in figure 11d may be up to 2cm.

In an alternative embodiment, the impact member is a single large bead which is not fixed to the walls of the outer tube 52 but is too large to pass through the outlet from that tube. Thus the bead is free to move within the tube 52 thereby generating additional turbulence. In that embodiment, the outlet of the tube 52 must be configured so that the bead cannot seal it, thereby blocking the apparatus.

Figures 12a and 12b show a chamber 58 arranged downstream of the dispersal device (not shown) and upstream of the mouthpiece (not shown). The chamber 58 has, at opposite ends, an inlet 59 and an outlet 60 for entry and exit of the dispersion. The chamber has a circular cross section and the inlet 59 is arranged in the side of the chamber tangentially to the axis of the chamber 58 so that the dispersion flows in a swirling, helical manner (as indicated by the dotted arrows) along the length of the chamber to the outlet 60 which is centrally located at the far end of the chamber 58. The walls of the chamber 58 taper inwards toward the outlet 60 in order to minimise "dead space" where powder may be deposited.

Immediately downstream of the outlet 60 is an impact member 60a upon which the dispersion impinges as it flows from the outlet 60. Impact member 60a is in the form of a cylinder arranged coaxially with the chamber 58 and having angled shoulders at its upstream end.

In a modified version of the apparatus shown in Figures 12a and 12b, the chamber 58 is cylindrical (without a taper at one end) and the exit from the chamber is arranged tangentially in the curved wall of the chamber 58 at the position shown by arrow A in Figures 12a and 12b.

In a further variation of the apparatus shown in Figures 12a and 12b, the chamber 58 may be part of the dispersal device. In this embodiment, the inlet 59 is an inlet for gas (rather then for dispersion) and communicates with the gas source. Powder is introduced into the chamber in the vicinity of the gas inlet through a separate powder inlet at the position marked with the arrow B in Figures 12a and 12b.

Figures 13a and 13b show partial views of a chamber 61 which is, with the exception of the inlet, generally similar to the chamber 58 shown in figures 12a and 12b. The chamber 61 has a tubular inlet 62 for the dispersion which meets the side wall of the chamber in a tangential way and which projects into the chamber 61. The end 63 of the inlet tube 62 which projects into the chamber 61 is closed and an open ended tube 64 is provided which extends through the wall of tube 62. Open ended tube 64 is angled to point in a slightly downstream direction. In use, a spiralling motion is imparted to the dispersion as it flows downstream along the length of the chamber 61.

An impact member (not shown) may be arranged immediately downstream of the chambers shown in Figures 12a, 12b, 13a and 13b.

Figures 14a and 14b show a chamber 65 of circular cross section having a tangentially arranged inlet 66. Outlet tube 67 is arranged at the same end of the chamber 65 as the inlet 66 but extends past that inlet 66 into the central portion of the chamber 65. Towards the other end of the chamber 65, the walls taper inwards to a second outlet 68 which opens into

collection chamber 69. In use, the gas/powder dispersion flows into the chamber 65 via inlet 66 and swirls around the interior of the chamber in a generally helical way as indicated by the dotted line and then out through the outlet tube 67. The chamber 65 acts as a cyclone to separate the small active particles, which are carried out towards the mouthpiece (not shown) through the tube 67, from large carrier particles or aggregates which are retained in the collection chamber 69.

Figures 15a and 15b show a further chamber 70 of circular cross section also having a tangentially arranged inlet 71. Coaxial with the chamber 70 is an inner chamber 72 also of circular cross section having at one end an outlet 73 and at the other end, in the region of the inlet 71, an opening 74 having three angled blades 75. In use, the dispersion enters the chamber 70 via inlet 71 and then flows into inner chamber 72 via opening 74 with angled blades 75 serving to impact a swirling, helical motion. In an alternative embodiment, the opening 74 extends all the way round the wall of the inner chamber 72 with the blades 75 being arranged at regular intervals.

Whilst the chambers of figures 12a, 12b, 13a, 13b, 15a and 15b have been described above as being downstream of the dispersal device so that gas/powder dispersion flows through them, they may also be arranged upstream so that the jet of gas flows through them before impinging on the powder. In this way a helical motion is imparted to the jet of gas which may persist when the powder has been entrained. In those arrangements, deposition of powder in the chambers is avoided.

Figure 16 shows a dispersal device similar to that shown in figure 10 having an impact member of the sort shown in figure 11d. The upstream end of outer tube 52 is open and is provided with two internal helical baffles 76 which extend

from the inside wall of tube 52 to touch the outside of narrow tube 51 thereby defining two helical air flow passages 76a. Figure 17 shows the view through line 1 shown in figure 16 looking right to left. In use, air is drawn in through the two helical air flow passages 76a and thereby adopts a helical, swirling motion which gives a high level of turbulance in the region around end 53 of tube 51 thereby promoting deagglomeration of the powder particles.

Figure 18 shows a tube 77 arranged between the dispersal device and the mouthpiece (not shown) having a helical section 78. In use, the dispersion flows through the tube in the direction of the arrow and a helical motion is imparted by the helical section 78. Surprisingly, the helical motion has been found to be imparted to the dispersion upstream of the helical section 78 as well as downstream.

Figure 19 shows an arrangement generally corresponding to that shown in figures 10 and 16 but wherein the outer tube 52 has an expanded portion 79 in the region of the impact member. That arrangement gives more room for the dispersion to pass around the impact member thereby reducing contact between the particles in the dispersion and the walls of the tube 52.

Figure 20 shows a package 80 of generally cuboidal form having within its upper face a trough shaped depression 81 (shown in broken lines) which runs along the length of the package. The trough 81 is of generally U-shaped cross-section in a plane perpendicular to the length of the package and meets with the upper face of the package to form a rectangular opening which is sealed over by foil covering 82. A pre-metered dose of powder 83 rests in the bottom of depression 81.

When it is desired to use the inhaler, the package 80 is fitted into the inhaler ready for use so that foil seal 82 is adjacent inlet tube 84 and outlet tube 85 as shown in Figure

20. Upon actuation of the inhaler, inlet tube 84 and outlet tube 85 move downwards, penetrating the foil covering 82 at diagonally opposed corners. The jet of gas flows from a reservoir (not shown) charged with propellant, through inlet tube 84 into the depression 81 and flows in a helical fashion as shown in Figure 20 entraining powder 83 to form a dispersion. The dispersion flows out of outlet tube 85 and then impinges on an impact member (not shown) prior to leaving the inhaler via the mouthpiece (not shown). After use the package 80 is removed from the inhaler. The inlet tubes 84 and 85 may be of any shaped cross-section, for example, square cross-section, but are conveniently cylindrical.

Figure 21a shows a side view of a package 86 also of cuboidal form. The package 86 has an internal chamber 87 (shown in broken lines) of cylindrical form running along the length of the package 86 and containing a pre-metered dose of powder 88. The chamber 87 is closed apart from inlet orifice 89 and exit orifice 90 and which are located approximately at opposite corners of the same side face of the package 86 and communicate with the chamber 87 via passages which open into the chamber in a tangential fashion.

When it is desired to use the inhaler, the package 86 is fitted on to the inhaler (see Fig 21b) such that inlet tube 91 (which is downstream of a reservoir of propellant which is not shown in Figure 21b) engages with inlet orifice 89 and outlet tube 92 (which communicates with a mouthpiece which is not shown in Figure 21b) engages with outlet orifice 90. Upon actuation of the inhaler, the jet of gas flows through inlet tube 91 and inlet orifice 89 into the chamber 87 and flows down the chamber in a helical fashion as shown in Figure 21b, thereby entraining the powder 88 to form a dispersion. The dispersion leaves the chamber 87 via outlet orifice 90 and outlet tube 92, and impinges upon an impact member (not shown)

and is then inhaled by the user via the mouthpiece (not shown). After use, the package 86 is detached from the inhaler.

Figures 22a and 22b show another package 93 of cuboidal form having a cylindrical chamber 94. The axis of the chamber is approximately vertical when in use and the diameter of the chamber is approximately twice its depth. At its lower end, the chamber 94 is closed by floor 95 upon which rests a pre-metered dose of powder 96. The wall of the chamber 94 is provided with inlet orifice 97 which communicates via a right-angled passage 98 with opening 99 in the upper face 100 of the package 93. The chamber 94 at its upper end also opens out to form a circular opening 101 in upper face 100 of the package 93.

Both of the openings 99 and 101 in the upper face 100 of the package 93 are sealed by foil patch 102 which covers most of upper face 100.

When it is desired to use the inhaler, the package 93 is fitted into the inhaler so that the openings 99 and 101 are directly beneath inlet tube 103 and outlet tube 104, respectively. The ends of the inlet and outlet tubes are sharpened for easier penetration of foil patch 102. Upon actuation of the inhaler, inlet tube 10 moves downward, piercing the foil patch 102 and entering passage 98. Outlet tube 104 also moves downward, piecing the foil patch and entering the chamber 94 along its axis.

A jet of gas flows through the inlet tube 103 and into the chamber 94 via passage 98 and inlet orifice 97. The jet of gas enters the chamber 94 in a tangential fashion and circulates around the chamber in a helical manner as shown in Figure 22b. The powder is entrained and also moves in a helical fashion with larger particles, for example, carrier particles, 105 being forced by centrifugal effect toward the

periphery of the chamber 94 whilst small inhalable drug particles gather in the axial region of the chamber 94 and are swept out of the outlet tube 104 onto an impact member (not shown) and then toward the mouthpiece (not shown). Thus, the larger particles are retained in the chamber 94 of the package 93 and are discarded along with that package after use of the inhaler.

Claims

1. A powder inhaler comprising dispensing means for making a dose of a powder available for dispersal, means for generating a jet of gas which, in use, impinges upon or flows across the powder thereby forming a dispersion of the powder in the gas, an impact member located downstream of the means for generating a jet of gas and a mouthpiece located downstream of the impact member.

2. An inhaler as claimed in claim 1, wherein the arrangement is such that, in use of the inhaler, the dispersion is formed during the period in which the user of the inhaler inhales from the inhaler.

3. An inhaler as claimed in claim 1 or claim 2, wherein the means for generating a jet of gas comprises a reservoir of liquid propellant and an exit valve.

4. An inhaler as claimed in claim 3, in which the exit valve is arranged to release vapour from the headspace above the liquid propellant.

5. An inhaler as claimed in claim 3 or claim 4, wherein the liquid propellant comprises a hydrofluoroalkane.

6. An inhaler as claimed in any of claims 1 to 5 in which the total internal volume of the parts of the inhaler through which, in use, the dispersion flows is less than 100 cm^3.

7. An inhaler as claimed in any of claims 1 to 6, in which, in use, choked flow conditions occur in the vicinity of, or downstream of, the zone where the jet of gas impinges on or flows across the powder.

8. An inhaler as claimed in claim 7, in which, in use, the jet of gas is generated by allowing the gas to pass through an orifice under conditions of choked flow from a region of high pressure to a region of low pressure.

9. An inhaler as claimed in any of claims 1 to 7, in which the shape, size and location of the impact member are such that it occupies a space through which at least 50% of the particles would otherwise pass.

10. An inhaler as claimed in any of claims 1 to 9 which comprises, downstream of the means of generating a jet of gas and upstream of the impact member, a tube of reduced internal diameter through which, in use, the dispersion flows, the outlet of the tube being directly upstream of the impact member and arranged to direct the flow onto the impact member.

11. An inhaler as claimed in any of claims 1 to 10, in which the inhaler comprises means for generating two or more jets of gas.

12. An inhaler as claimed in any of claims 1 to 11, which also comprises an air inlet which communicates with the zone where the jet of gas impinges or flows across the powder and with the mouthpiece, the arrangement being such that, in use, both the dispersion of the powder in the gas and air from the atmosphere are combined and are inhaled simultaneously by the user.

13. An inhaler as claimed in any one of claims 1 to 12 in which the dispensing means for making a dose of powder available for dispersal is arranged to make available pre-metered doses of powder.

14. An inhaler as claimed in claim 13 in which the dispensing means comprises an inlet tube and an outlet tube, the arrangement being such that, in use of the inhaler, the jet of gas flows through the inlet tube into a package containing a pre-metered dose of powder and the dispersion flows out of the package through the outlet tube.

15. An inhaler as claimed in claim 14 in which one or both of the inlet and outlet tubes are arranged, in use, to cooperate with preformed orifices in the package.

16. An inhaler as claimed in claim 14 or claim 15 in which one or both of the inlet and outlet tubes are arranged to be movable so as to penetrate, in use, a penetrable wall of the package.

17. An inhaler as claimed in any one of claims 1 to 13, which comprises a reservoir for holding the powder and in which the dispensing means comprises metering means for metering individual doses of powder from the reservoir.

18. An inhaler as claimed in any one of claims 1 to 17, in which the dispensing means comprises a feed device for incremental feeding of the powder, in use, into the jet of gas.

19. An inhaler as claimed in claim 18, wherein the feed device comprises a linear or circular strip for holding the powder and which, in use, moves through the jet of gas.

20. An inhaler as claimed in claim 19 in which the strip is textured to hold powder.

21. An inhaler as claimed in claim 18, in which the powder is held in a holder and the feed means comprises a plunger which, in use, pushes the powder from the holder.

22. An inhaler as claimed in any of claims 1 to 20 which comprises means for imparting a helical flow to the dispersion.

23. An inhaler as claimed in any of claims 1 to 20, which comprises a chamber containing a plurality of relatively large particles, the chamber having an inlet for the jet of gas, an inlet for the powder and an outlet, the inlets and the outlet having mesh means to retain the relatively large particles within the chamber and the arrangement being such that, in use, the gas agitates the relatively large particles.

24. An inhaler as claimed in any of claims 1 to 23, which comprises a chamber located downstream of the zone in which the jet of gas impinges upon or flows across the powder, the

chamber containing a plurality of relatively large particles and having an inlet through which, in use, the dispersion enters the chamber and an outlet through which, in use, the dispersion leaves the chamber, the inlet and outlet having mesh means to retain the relatively large particles within the chamber and the arrangement being such that, in use, the gas agitates the relatively large particles.

25. An inhaler as claimed in any of claims 1 to 24, which comprises, downstream of the zone in which the jet of gas impinges upon or flows across the powder, means for subjecting the dispersion, in use, to converging currents of gas.

26. An inhaler as claimed in any one of claims 1 to 25, which includes restriction means for restricting the flow rate through the mouthpiece to not more than 80 litres/min.

27. An inhaler as claimed in any of claims 1 to 26, which is actuated upon inhalation through the mouthpiece.

28. An inhaler as claimed in claim 27, in which the arrangement is such that upon inhalation through the mouthpiece the jet of gas is generated and continues to be generated for between 0.1 and 5 seconds.

29. An inhaler as claimed in any of claims 1 to 28, in which the mouthpiece is adapted to extend, in use, past the teeth of the user and over at least a portion of the user's tongue.

30. An inhaler as claimed in claim 29, in which the mouthpiece comprises external stop members which, in use, abut the lips or the teeth of the user.

31. A powder inhaler comprising dispensing means for dispensing a dose of a powder, a dispersal device comprising means for generating a jet of gas which, in use, impinges upon or flows across the powder thereby forming a dispersion of the powder in the gas and a mouthpiece located downstream of and communicating with the dispersal device, the arrangement being such that, in use of the inhaler, the dispersion is formed

during the period over which the user of the inhaler inhales from the inhaler.

32. An inhaler substantially as described herein with reference to Figures 1 to 5, 6a-c, 7 to 9, 10a, 10b, 11a-d, 12a, 12b, 13a, 13b, 14a, 14b, 15a, 15b, 16-20, 21a, 21b, 22a and 22b.

33. A package for use with an inhaler as claimed in any of claims 13 to 16 which contains a pre-metered dose of powder and has inlet and outlet orifices.

34. A package for use in an inhaler as claimed in any of claims 13 to 16 which contains a pre-metered dose of powder and has at least one penetrable wall.

35. A package for use in an inhaler as claimed in any of claims 13 to 16 which contains a pre-metered dose of powder and comprises means for imparting, in use, a helical flow to the dispersion.

36. A method of generating a dispersion in a powder inhaler comprising the steps of

1) making a dose of powder available for dispersal;

2) generating a jet of gas under positive pressure which impinges upon or flows across a powder thereby forming a dispersion of the powder in the gas; and

3) directing the flow of the dispersion onto an impact member.

37. A method as claimed in claim 36, wherein the dispersion is formed during the period over which the user of the inhaler inhales from the inhaler.

38. A method as claimed in claim 36 or claim 37, in which the jet of gas is generated by allowing gas at a pressure above atmospheric to flow through an orifice to a region of atmospheric pressure.

39. A method as claimed in any of claims 36 to 38 in which the jet of gas comprises the vapour of one or more propellants known for use with pressurised metered dose inhalers.

40. A method as claimed in claim 36 or claim 37, in which the jet of gas is a jet of air.

41. A method as claimed in any of claims 36 to 37, in which the jet of gas and/or the dispersion experiences choked flow conditions.

42. A method as claimed in any of claims 36 to 41, which also comprises the step of combining the dispersion with air drawn into the inhaler by the user.

43. A method as claimed in any of claims 36 to 42 in which inhalation through the inhaler actuates the generation of the jet of gas.

44. A method for generating a dispersion in a powder inhaler substantially as described herein with reference to any of Figures 1 to 5, 6a-c, 7 to 9, 10a, 10b, 11a-d, 12a, 12b, 13a, 13b, 14a, 14b, 15a, 15b, 16-20, 21a, 21b, 22a and 22b.

Fig.1.

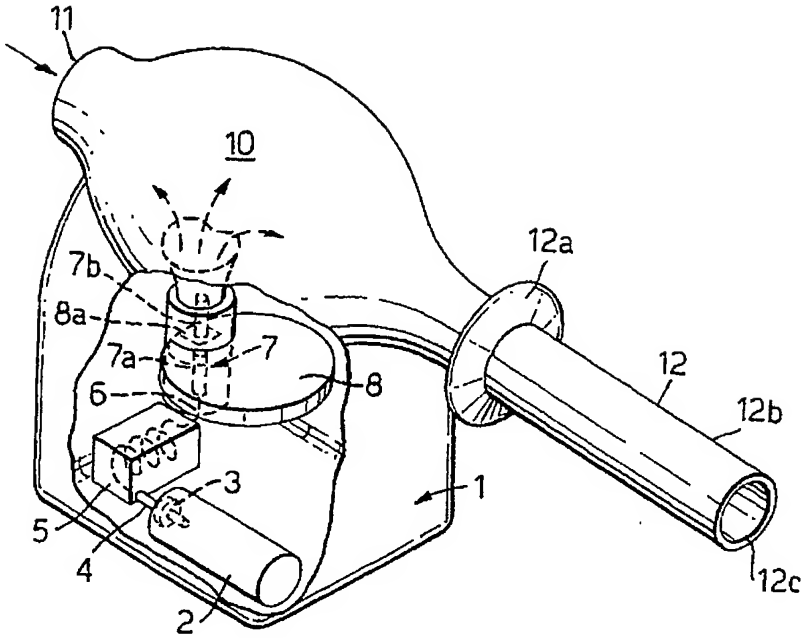


Fig.2.

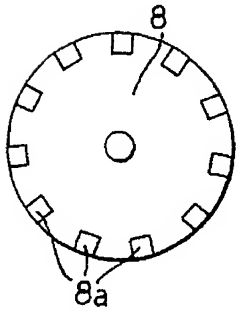


Fig.3.

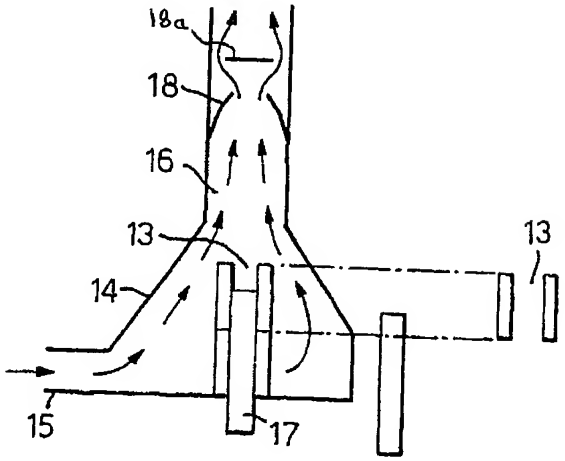


Fig.4.

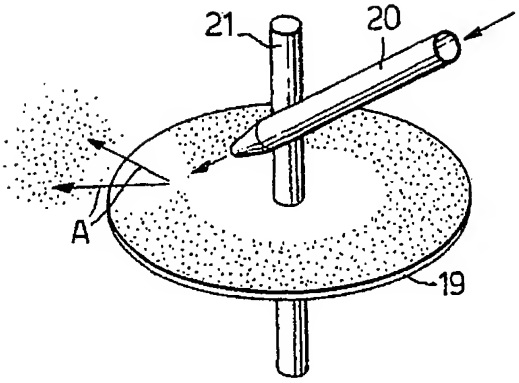


Fig.5.

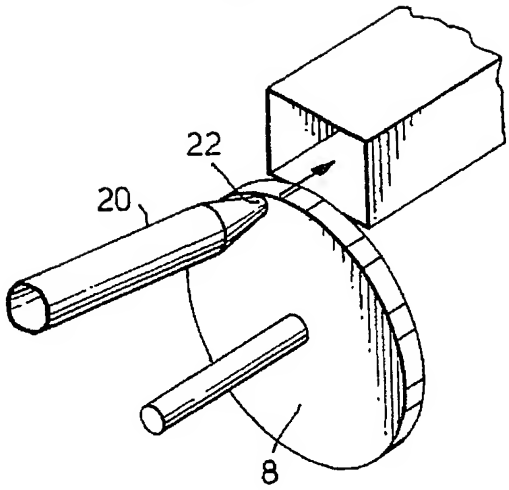


Fig.6a.

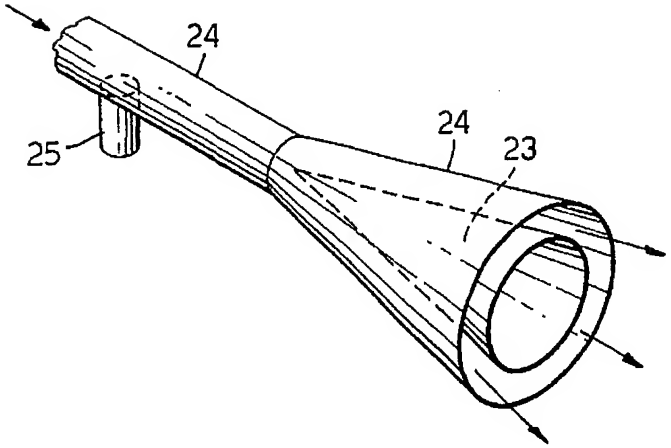


Fig.6b.

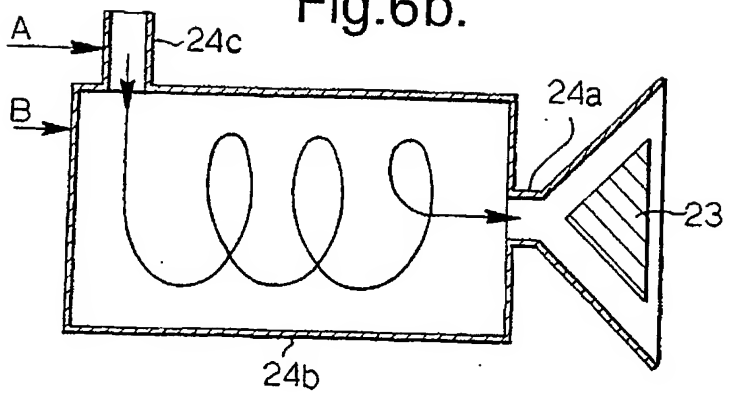


Fig.6c.

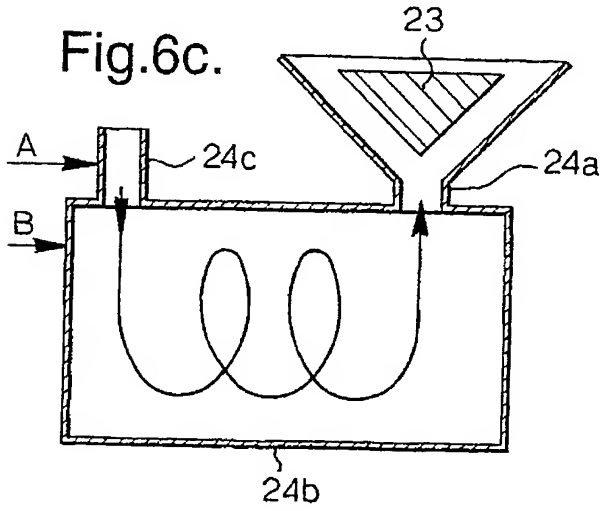


Fig.7.

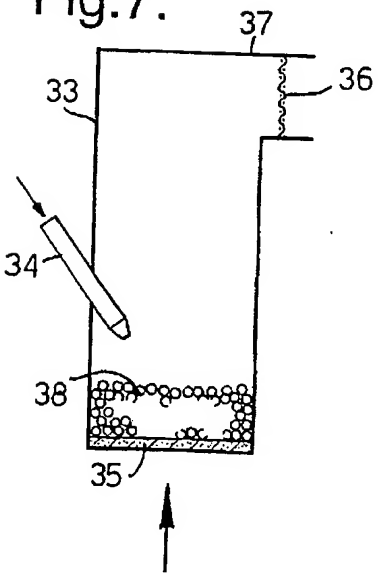


Fig.8.

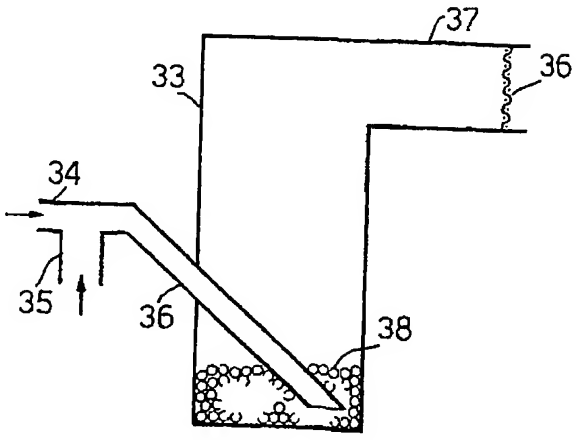


Fig.9.

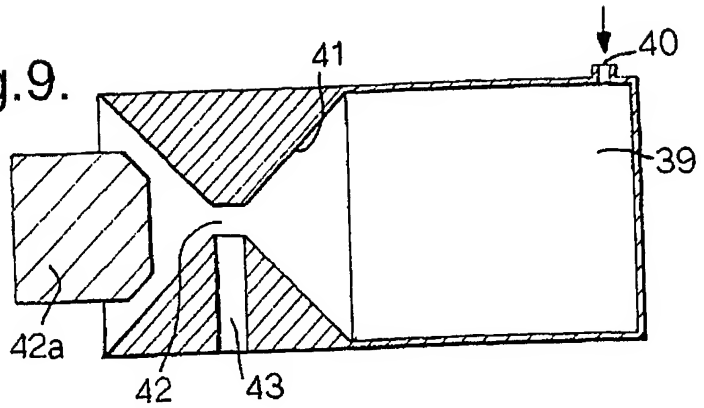


Fig.10a.

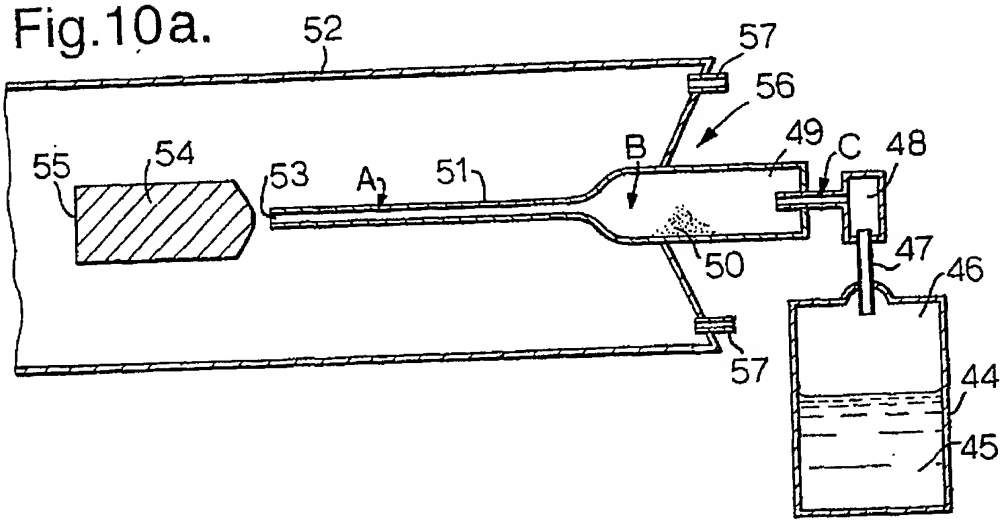


Fig.10b.

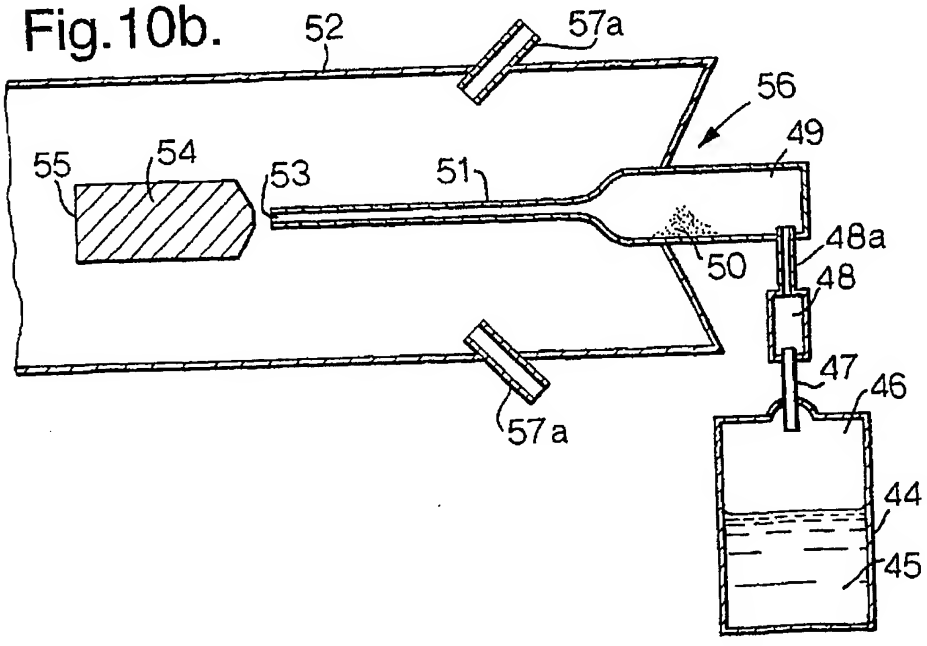


Fig.11a.

Fig.11b.

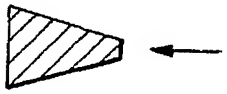
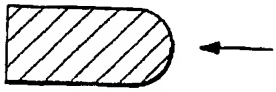


Fig.11c.



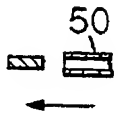


Fig.11d.

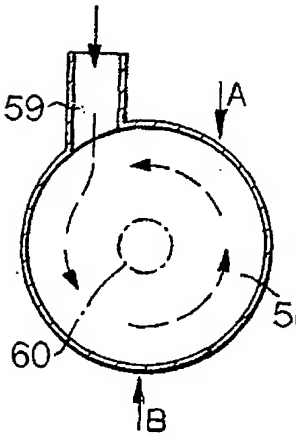
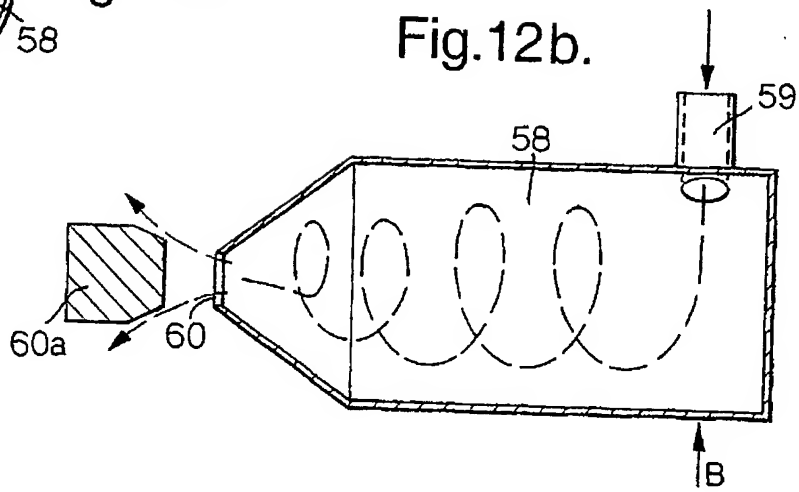


Fig.12a.

Fig.12b.



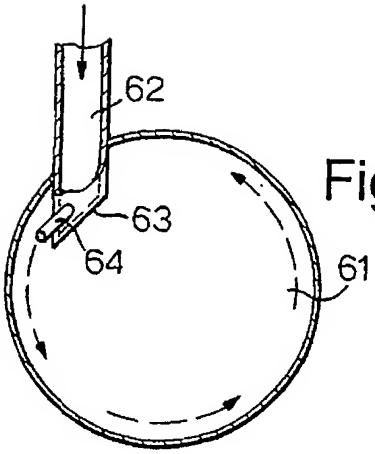


Fig.13a.

Fig.13b.

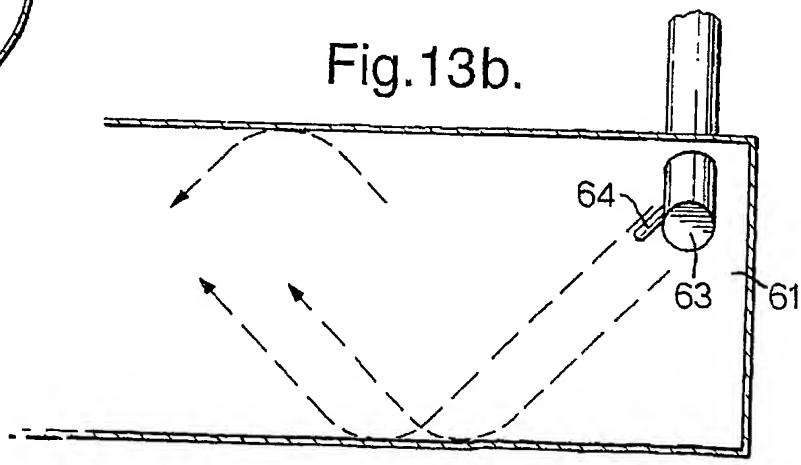


Fig.14a.

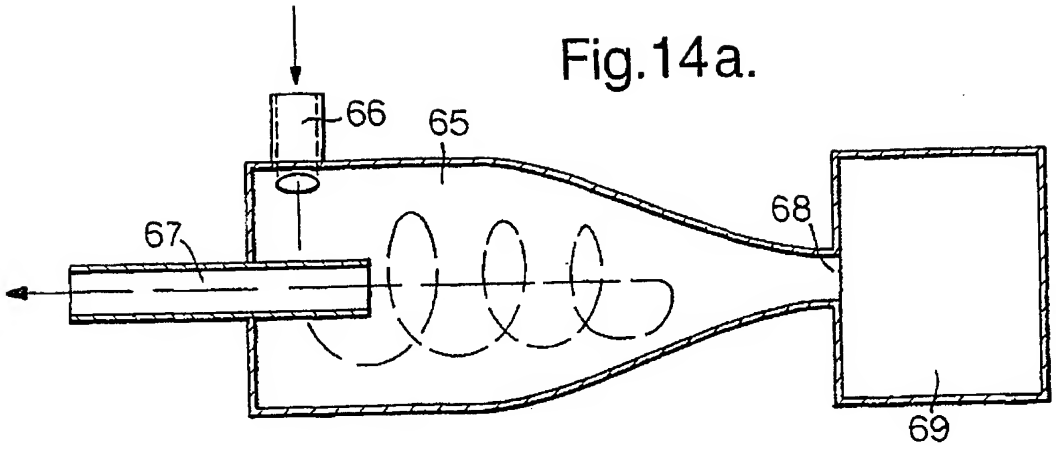


Fig.14b.

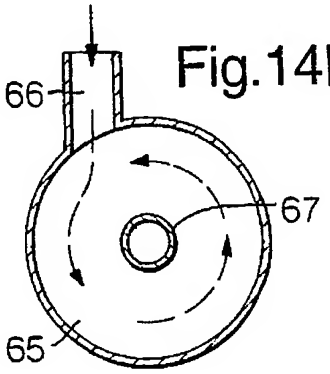


Fig.15a.

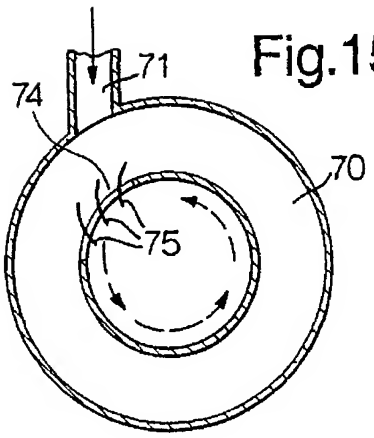
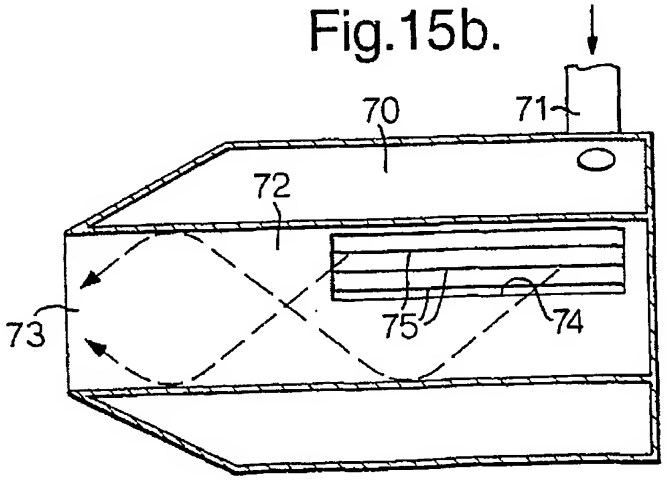


Fig.15b.



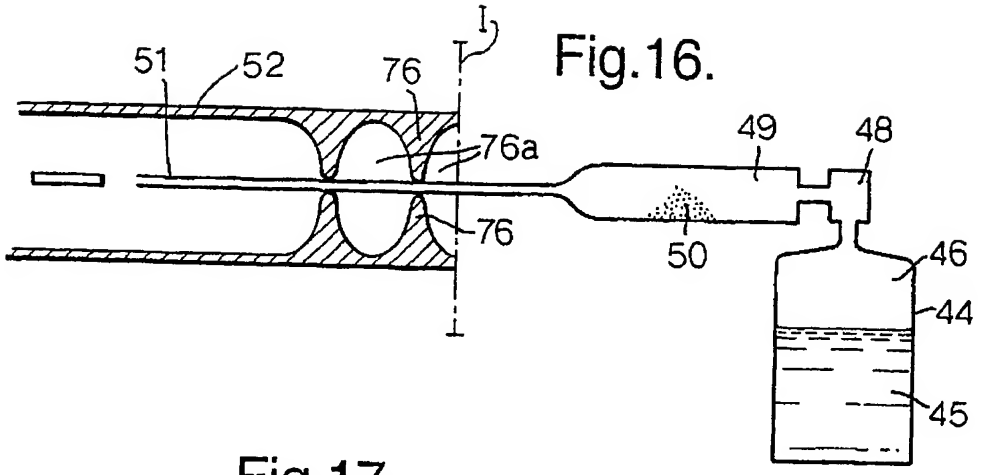


Fig.16.

Fig.17.

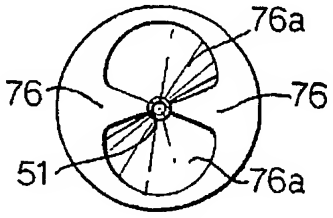
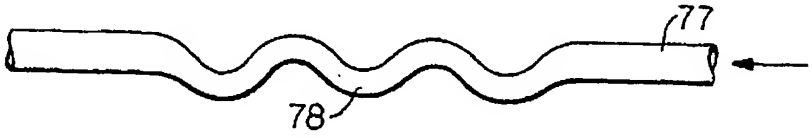


Fig.18.



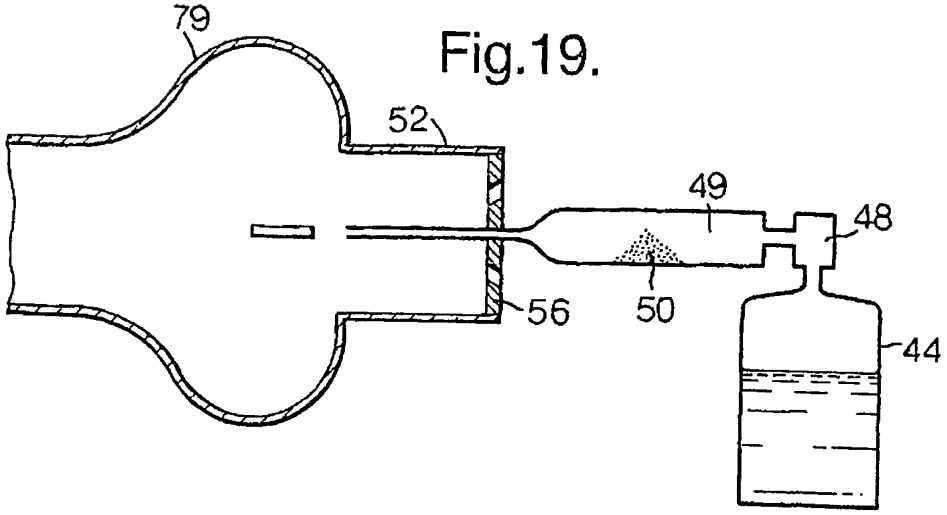


Fig.19.

Fig.20.

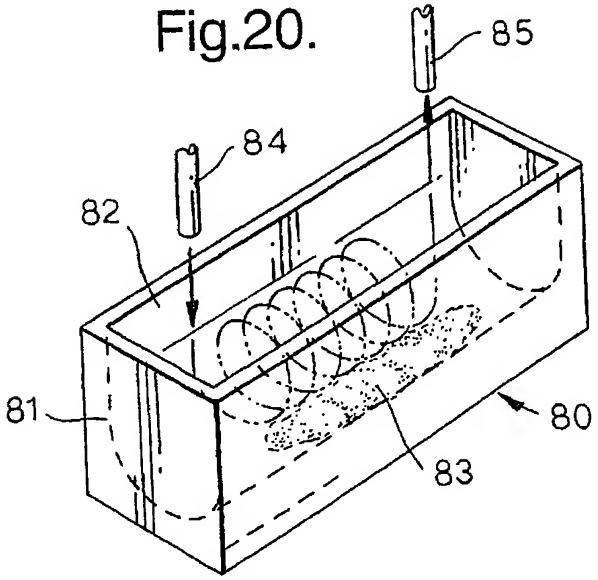


Fig.21a.

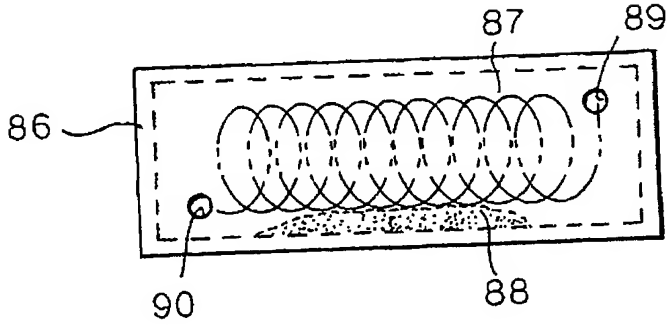


Fig.21b.

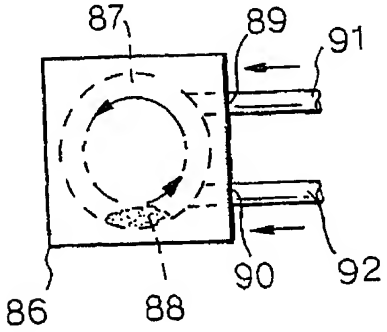


Fig.22a.

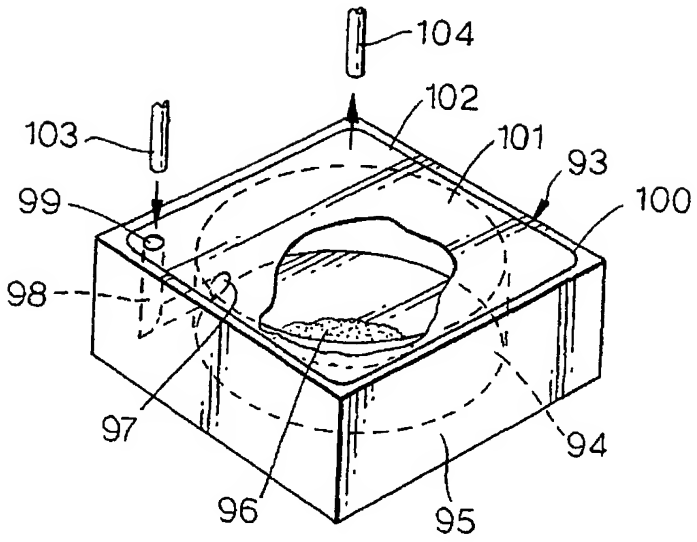
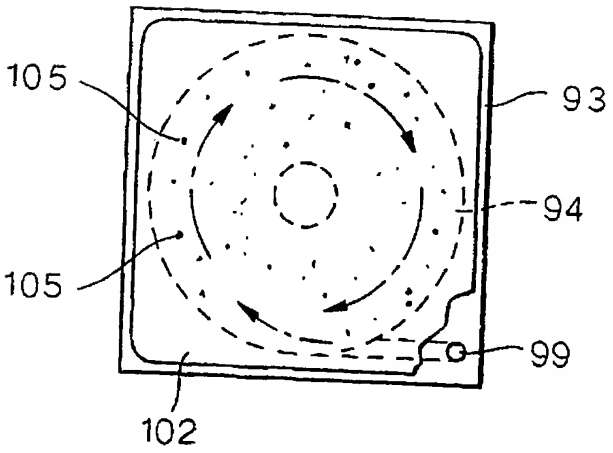


Fig.22b.



INTERNATIONAL SEARCH REPORT

PCT/GB 02/00198

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 524 613 A (SMEDLEY WILLIAM H ET AL) 11 June 1996 (1996-06-11) claims 1,2,4,7,22; figure 5	1,2,9, 10,12, 17,18, 21,25, 27,28, 31,32
X	WO 90 15635 A (HUHTAMAEKI OY) 27 December 1990 (1990-12-27)	33-35
Y	abstract; figures 6A-6C	15,16,22
X	US 3 998 226 A (HARRIS ARTHUR M) 21 December 1976 (1976-12-21)	1,3-6, 10-14, 29-31
Y	claims; figures	15,16, 22-24

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2002	24/06/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Villeneuve, J-M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/GB 02/00198

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 740 794 A (BURR JOHN D ET AL) 21 April 1998 (1998-04-21) abstract; figure 1	1,18-20
A	column 13, paragraph 4	
A	US 5 676 130 A (GUPTE ARUN RAJARAM ET AL) 14 October 1997 (1997-10-14) figures	7,8 1,9,10
Y	US 3 653 380 A (HANSEN LLOYD FRANK) 4 April 1972 (1972-04-04) column 3, line 15 - line 30; figures	23,24
A	US 5 642 727 A (DATTA PABITRA ET AL) 1 July 1997 (1997-07-01) abstract; figures	23,24
A	US 4 534 345 A (WETTERLIN KJELL I L) 13 August 1985 (1985-08-13)	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/GB 02/00198

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 36-44
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/00198

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5524613 A	11-06-1996	AU 7637694 A	22-03-1995
		WO 9506491 A2	09-03-1995
WO 9015635 A	27-12-1990	FI 892956 A	17-12-1990
		AT 195434 T	15-09-2000
		AU 641659 B2	30-09-1993
		AU 5746990 A	08-01-1991
		BR 9007440 A	28-04-1992
		CA 2058954 A1	14-12-1991
		DE 69033607 D1	21-09-2000
		DE 69033607 T2	28-12-2000
		DK 477222 T3	18-12-2000
		EP 0477222 A1	01-04-1992
		ES 2150412 T3	01-12-2000
		WO 9015635 A1	27-12-1990
		HK 1011298 A1	29-12-2000
		HU 213187 B	28-03-1997
		JP 4506018 T	22-10-1992
		KR 9411441 B1	15-12-1994
		MX 173780 B	25-03-1994
		NO 303528 B1	27-07-1998
		NZ 234031 A	26-10-1993
		RU 2089227 C1	10-09-1997
US 3998226 A	21-12-1976	GB 1505608 A	30-03-1978
		JP 912368 C	21-07-1978
		JP 52039990 A	28-03-1977
		JP 52040795 B	14-10-1977
US 5740794 A	21-04-1998	US 5785049 A	28-07-1998
		AU 697676 B2	15-10-1998
		AU 3553295 A	09-04-1996
		BR 9508964 A	02-06-1998
		CA 2200727 A1	28-03-1996
		CN 1160358 A	24-09-1997
		CZ 9700723 A3	12-11-1997
		EP 0846009 A1	10-06-1998
		FI 971173 A	20-03-1997
		HU 77691 A2	28-07-1998
		IL 115369 A	29-06-2000
		JP 10508790 T	02-09-1998
		NO 971316 A	20-05-1997
		NZ 293163 A	24-09-1998
		NZ 331353 A	29-07-1999
		PL 319505 A1	18-08-1997
		RU 2146153 C1	10-03-2000
		US 6089228 A	18-07-2000
		WO 9609085 A1	28-03-1996
		US 6372258 B1	16-04-2002
		ZA 9507933 A	02-08-1996
US 5676130 A	14-10-1997	DE 4208880 A1	23-09-1993
		AT 189125 T	15-02-2000
		AU 680191 B2	24-07-1997
		AU 3747993 A	21-10-1993
		BR 9306112 A	13-01-1998
		CA 2131544 A1	30-09-1993
		CZ 9402285 A3	18-01-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/00198

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5676130 A		DE	59309940 D1	02-03-2000
		DK	633792 T3	10-07-2000
		WO	9318811 A1	30-09-1993
		EP	0633792 A1	18-01-1995
		ES	2141149 T3	16-03-2000
		FI	944297 A	16-09-1994
		GR	3033041 T3	31-08-2000
		HU	69417 A2	28-09-1995
		JP	3223300 B2	29-10-2001
		JP	8500743 T	30-01-1996
		KR	272385 B1	15-11-2000
		NO	943463 A	16-09-1994
		NZ	249846 A	24-02-1997
		PL	171269 B1	28-03-1997
		PT	633792 T	28-04-2000
		RU	2101036 C1	10-01-1998
		SK	110794 A3	08-02-1995
US 3653380 A	04-04-1972	AT	330951 B	26-07-1976
		AT	128471 A	15-10-1975
		BE	762948 A1	16-08-1971
		CA	982005 A1	20-01-1976
		CH	536119 A	30-04-1973
		DE	2106794 A1	26-08-1971
		DK	132012 B	13-10-1975
		ES	194458 Y	01-04-1975
		FR	2078678 A5	05-11-1971
		GB	1305172 A	31-01-1973
		HK	13176 A	19-03-1976
		JP	56001102 B	12-01-1981
		MY	7776 A	31-12-1976
		NL	7101065 A ,B,	18-08-1971
		SE	381180 B	01-12-1975
		US	3809084 A	07-05-1974
		ZA	7100007 A	27-10-1971
US 5642727 A	01-07-1997	AU	6841996 A	26-02-1997
		CA	2227594 A1	13-02-1997
		EP	0840631 A1	13-05-1998
		JP	11510074 T	07-09-1999
		WO	9704827 A1	13-02-1997
US 4534345 A	13-08-1985	SE	438261 B	15-04-1985
		AT	386524 B	12-09-1988
		AT	265282 A	15-02-1988
		AU	576977 B2	08-09-1988
		AU	6692586 A	09-04-1987
		AU	560654 B2	16-04-1987
		AU	8560982 A	13-01-1983
		BE	893795 A1	10-01-1983
		CA	1178152 A1	20-11-1984
		CH	657054 A5	15-08-1986
		DE	3224562 A1	17-02-1983
		DK	304582 A	09-01-1983
		FR	2509181 A1	14-01-1983
		GB	2102295 A ,B	02-02-1983
		GB	2144997 A ,B	20-03-1985
		IT	1148984 B	03-12-1986

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/00198

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4534345 A		JP 58019268 A	04-02-1983
		LU 84256 A1	22-03-1984
		NL 8202676 A	01-02-1983
		NO 822371 A ,B,	10-01-1983
		NZ 201153 A	12-07-1985
		SE 8104240 A	09-01-1983
		SE 438262 B	15-04-1985
		SE 8204134 A	05-07-1982
		SE 460097 B	11-09-1989
		SE 8500757 A	18-02-1985
		SE 460098 B	11-09-1989
		SE 8500758 A	18-02-1985
		US 4667668 A	26-05-1987

Form PCT/ISA/210 (patent family annex) (July 1992)